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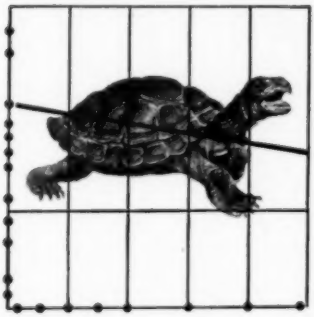

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*Thomas, E. W., et al: *J.A.M.A. 137:1517, 1948*

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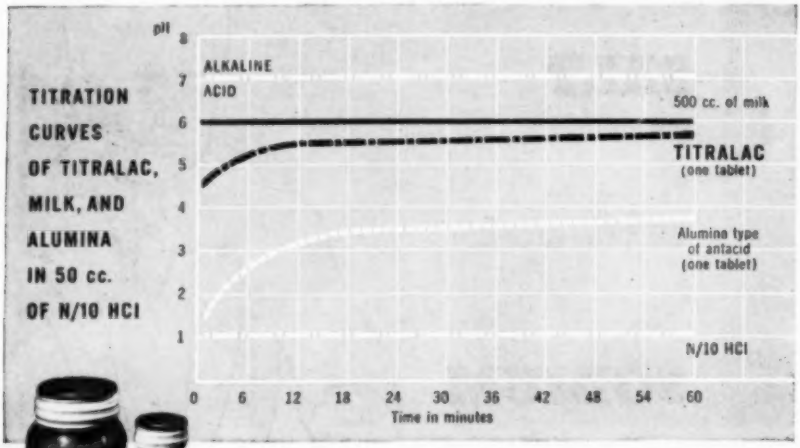

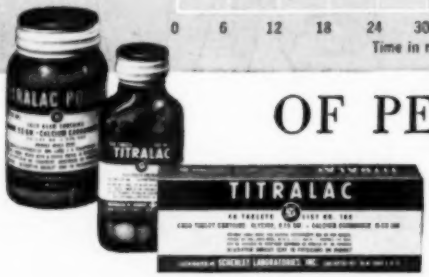

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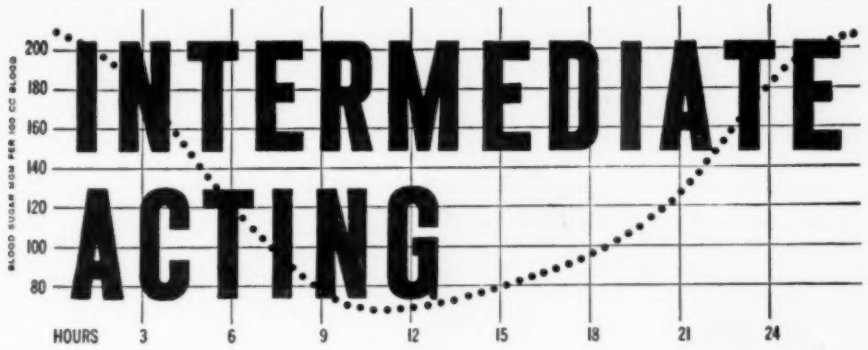

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ANNALS OF INTERNAL MEDICINE

VOLUME 31 JULY, 1949 NUMBER 1

THE INTERNIST, PAST, PRESENT AND FUTURE*

By WALTER W. PALMER, F.A.C.P., *New York, N. Y.*

IT is a pleasure to welcome the newly elected Fellows and Associates on this occasion. I am confident that you will enjoy and profit by the privileges and associations which come to you as members of the American College of Physicians.

In keeping with tradition, the retiring President is expected to address the Convocation on some phase of medicine which may be of interest or importance to the welfare of the College. Several of my distinguished predecessors on these occasions have presented their ideas of the characteristics, abilities, qualities and responsibilities of the internist. This evening I propose to direct a few remarks to factors important in the training of the internist and the institutions upon which maintenance of his high standards depends. I have in mind the welfare of the university clinic, which has played such an important rôle in the progress of medicine during the last half-century.

Fifty years ago, the general practitioner predominated throughout the country. A complacent community respected and usually adored the equally complacent doctor who practiced with the confidence that all possible was being done for the patient. A few physicians in large cities, after years of general practice and arriving at the fashionable and famous stage, confined their practice to internal medicine. Practice was relatively simple. Nearly all of the laboratory tests could be performed at the bedside. Except for surgical cases, there was small provision made for private patients in hospitals. In serious illness, profound pronouncements from the hierarchy were final and sufficient. The situation is far different today.

The first significant event leading to what we regard as modern medicine was the opening of the Johns Hopkins Medical School in 1893, with Dr. William H. Welch as Dean and Professor of Bacteriology. Dr. Welch had recently returned from Germany after two years' study with Ludwig, Cohnheim and other medical scientists. He and his early associates, especially

* Presidential Address, Annual Convocation, Thirtieth Annual Session, American College of Physicians, New York, N. Y., March 30, 1949.

Mall, were convinced that a clinic where a scientific approach to problems of the sick could be made was extremely desirable. Then came the development of the Rockefeller Institute for Medical Research in 1901–1906, with Dr. Simon Flexner as Director and, in 1910, the Hospital, with Dr. Rufus Cole as Director; then, the organization of the Council on Medical Education by the American Medical Association in 1905; also, the report on the state of the medical schools by Mr. Abraham Flexner in 1909 in which he called attention to the need of scientists in the clinical department; finally, in 1914, Johns Hopkins inaugurated a full-time system with Theodore Janeway as Chief of Medicine, William S. Halsted as Chief of Surgery and John Howland as Chief of Pediatrics.

In 1921, Columbia University became affiliated with the Presbyterian Hospital here in New York for the purpose of developing a Medical Center, with Medicine and Surgery organized as university departments. It was my privilege to occupy the Chair of Medicine. Within a decade, Yale, Cornell, Rochester, Western Reserve, Chicago, Washington and Vanderbilt had organized full-time clinical departments, and others had adopted modifications of it. It was impossible for all medical schools to change their type of organization. The expense was considerable and suitable personnel was not readily available. However, the influence of the university clinic has been far-reaching so that now, every teaching unit in the country is equipped with diagnostic laboratories and maintains various research facilities, with young men on a full-time arrangement.

It was a thrilling experience for me to spend two years (1915 to 1917) at the Rockefeller Hospital where, for the first time in this country, young men had an opportunity to get training in clinical science. Here were patients cared for under ideal hospital conditions and selected because of the disease which was under special study. Here were well-equipped laboratories where elaborate methods could be employed to study underlying derangements of disease. Here were provisions for animals and animal experimentation. Here, chemists, bacteriologists and physiologists could collaborate with physicians in a concentrated enterprise. The value of such an organization was early demonstrated in the now famous work on pneumonia. Within five years, the pneumococcus had been typed and a potent anti-serum for type I developed which dramatically reduced the mortality for this type from 30 per cent to less than 10 per cent. The treatment of pneumonia with anti-pneumococcic serum now belongs to history. That serum therapy has been largely superseded by antibiotics does not detract in any way from the stimulus that these early studies gave to medicine as a science. No single influence on the growth and development of the university clinic has been as great as the example of the Rockefeller Hospital under the leadership of Dr. Cole. When that institution celebrated its twentieth anniversary, 56 of its former associates occupied full-time professorial posts scattered throughout this and other countries. Thirty-one men were in junior full-time teaching and research positions.

The numerous scientific contributions made by the university clinics and research institutes have led to the development of a large number (over 100) of bacterial, chemical and physiological tests. Many are aids in the diagnosis or understanding of altered function in disease processes, others are necessary for the intelligent and safe use of important therapeutic measures. The introduction of these elaborate and complicated technics has added difficulties both to the education of the student and to the practice of sound medicine.

The best training is found in a clinic where the highest type of medical practice is exhibited and where there is a group actively engaged in clinical research. The staff of such a clinic should be comprised of individuals of varied interests and capabilities. Of prime importance is a group of full-time men, the Chief and Assistants, of varying ages, relatively small, but who set the pace and standards for the department. Their entire time should be taken up in care of the sick, teaching and research but without the responsibilities and interruptions of private practice. Within this group should be included the occasional investigator who desires and has the ability to make clinical science a career. Such a person must be assured of security and freedom; must be free of routine; must be able to take care of the sick people necessary for his studies and his teaching abilities used wisely. Close association with the preclinical departments is of great importance either through coöperation on individual problems or by assignment of staff members from one department to the other. The full-time group should constitute a functioning unit in which are included internes, residents and fellows who are in different phases of their training. Participating with the full-time members it is essential to have a large group of men of all ages, engaged in the practice of internal medicine, who should take an active part in the teaching and care of patients in the clinic. Through this group, both students and staff benefit by having the wisdom and experience derived from private practice brought to the clinic. The men in practice have the opportunity to follow, at first hand, the advances in medicine and often make valuable suggestions as to the direction in which special technics are to be applied. An organization of this type permits of considerable flexibility. It provides an opportunity for all to make contributions, whether their interests are directed toward practice or academic careers.

Essential for the internist in his early years is the development of an attitude of mind and a point of view. This requisite is acquired only when the daily task is imbued with the spirit of research. There should be the opportunity to watch the unraveling of problems which are under investigation. Nothing is more inspiring to the formative mind than the association with men of experience, native ability and with good training. The period in which to inculcate qualities necessary for good work—accuracy, thoroughness, critique and integrity—is during the early years.

One of the best justifications of modern medicine is the striking improvement in the accuracy of clinical diagnosis. In a study of several hundred

records at the Massachusetts General Hospital, Richard Cabot, in 1910, uncovered the disquieting fact that in only 20 per cent was the clinical diagnosis confirmed at the autopsy table. Now, in the good teaching clinics, 80 per cent or more clinical diagnoses are shown to be correct. To be added are the discoveries of many new etiological agents of disease and triumphs in treatment, such as insulin, liver extract, antibiotics and specific nutritional adjuvants. An illuminating and impressive catalog of the accomplishments of the past 50 years, in the control of chronic diseases, has been constructed by Dr. David Seegal and collaborators. In summary, the largely controlled chronic illnesses number 16; the partially controlled amount to 35 and a group of the uncontrolled remain; among which, of course, are arteriosclerosis, hypertension and neoplasms.

As medicine has advanced, practice has increased in scope and complexity. No longer can one man encompass all. This has inevitably led to group practice and specialization. Not only do we have the internist but the internist with his pet sub-specialty: cardiology, allergy, gastroenterology, endocrinology, diseases of the chest, arthritis and others—all with their national societies. Some apprehensive seers have suggested that internal medicine is in danger of sub-dividing to a point where the internist will be eliminated. This should never take place. Meetings such as these of the College are designed to enable each of us with our interests and avocations to listen to a widely diversified group of subjects so that we may all maintain the broad basic knowledge and training upon which our skill, self-confidence and sense of usefulness rest.

But, what of the future? Since the welfare of the internist is inextricably associated with medical progress, whatever affects one will have its influence on the other. In recent years, there have appeared on the horizon danger signals which, unless heeded, will have a devastating effect on the continuation of clinical research and the maintenance of the present high standards in the training of teachers and practitioners.

The most important single menace is the present critical situation of the university medical clinic. The burning question now is: "Can the University Clinic survive?" A major difficulty is insufficient funds, which forces key men into private practice in order to supplement their university stipends. In the face of almost daily announcements of large sums given for medical research, this statement might be challenged. However, these large gifts, amounting to several millions of dollars, have not brought much relief to the medical schools. Very little of this money, so far as I am aware, was given for general purposes which might aid in the stabilization of the scientific departments. A large percentage of the sums given for medical research was for special purposes on a short-term basis. Instead of serving to stabilize departments of medicine and other science departments in the medical schools, these gifts may prove embarrassing. Short-term grants for specific short-term projects attract into the field young, short-term men. With large sums as inducement, there is danger of shaping requests which find

favor with the recommending committees rather than for work in which the individual may have an especial ability. Short-term projects tend to increase quantity to the sacrifice of quality. I do not mean to imply that such funds cannot be useful. They can be! They provide for developmental research and for men to pursue advanced clinical studies while they acquire training in internal medicine. In recent years, large sums have become available for the investigation of specific diseases. As desirable as this may be, the elaborate and well-financed organizations set up for these studies have a tendency to drain the university of some of its key investigators and many of its younger scientists. On the other hand, many men who are not qualified by training or ability to make science a career are attracted by the availability of comfortable stipends. As I see it, the university, which serves as the base for training young men in science, is in danger because it cannot maintain its departments with adequate men and funds needed to support the superstructure just outlined. The Government and many non-Government agencies do not start young men in the beginning of their scientific careers. This is the business of the universities.

The firm foundation on which a university department is built is stable and dependable funds. Lack of substantial additions to endowments, reduced rates of interest on invested funds, war-time taxes and inflation have combined to reduce seriously the permanent funds of the universities. One of the greatest needs now is for additions to their dependable funds in order to provide more career positions in the basic sciences and clinical science. Not until such positions are created will bright young men be attracted to medical sciences.

In looking for a source of funds, which are so badly needed by the universities for their medical schools, the economic trends suggest Government funds. There has been a long-standing apprehension about accepting Government aid on the ground that it may lead to loss of control on the part of the university. The universities are now accepting large sums on a temporary basis. For the period January 1, 1946 to August 31, 1948, the United States Public Health Service reports nearly $20,000,000 given for medical research. The Army and Navy have made handsome contributions for similar purposes. A large share of these monies has gone to the universities. So far as I am aware, there is no complaint about control. A source of Government aid would seem to be a National Science Foundation. Bill S. 247, which provides for such a foundation, was recently reported out of committee and is based on the recommendations of the Bush Report of 1945. It would make available for the universities fluid funds which are so desperately needed at the moment.

Another powerful but uncertain influence, clearly linked with the financial difficulties of the medical schools, is the problem of medical care. This centers around distribution and cost, which has increased many fold. The comfort and life-saving measures which medical progress has provided should be available to the general population but not at the expense of medical prog-

ress itself. Our Country is large—our social organization complex—localities differ widely in their needs! While there is probably no perfect solution to this problem, it needs the most careful study by our ablest medical statesmen, who will need the aid of the economist, sociologist and political scientist in order to arrive at a reasonably satisfactory plan of action. The direction which this phase of our medical responsibilities takes will profoundly affect the progress of medicine.

We members of the College are vitally interested in maintaining the high level of medical practice made possible by the extraordinary advances of the past. We desire continuation and extension of the facilities which have brought about progress. However, no matter what happens to our hopes and aspirations, the ambitions, methods and work of the physician, as Osler described them, must remain the same: "To wrest from nature the secrets which have perplexed philosophers in all ages, to track to their sources the cause of disease, to correlate the vast stores of knowledge, that they may be quickly available for the prevention and cure of disease—these are our ambitions. To carefully observe the phenomena of life in all its phases, normal and perverted, to make perfect the most difficult of all the arts, the art of observation, to call to aid the science of experimentation, to cultivate the reasoning faculty, so as to be able to know the true from the false—these are our methods. To prevent disease, to relieve suffering and to heal the sick—this is our work."

THE HOSPITAL AS A CENTER OF PREVENTIVE MEDICINE *

By STANHOPE BAYNE-JONES, M.D., Sc.D. (hon.), President, Joint Administration Board, New York Hospital-Cornell Medical Center, *New York, N. Y.*

MR. PRESIDENT, Members of the American College of Physicians, and guests:

In selecting me to deliver the James D. Bruce Memorial Lecture on Preventive Medicine, the Board of Regents of the American College of Physicians has conferred upon me a distinguished honor. I am grateful for their favor and for the privilege of addressing the College at its Thirtieth Annual Session.

I realize that my opportunity to appear before you on this occasion comes not from any original contributions of my own to preventive medicine, medical education, or to the functions of hospitals in the social order, but to influences of heredity and the fortunate personal associations of a lifetime. I should like to acknowledge my indebtedness to many men to whom I owe the honor you have given me. It is not possible to speak of all of them, or even recall the sources in conferences and discussions of ideas and material that make the substance of this Lecture. Through your selection for this lectureship, however, some men are before you in spirit if not in person. The first in time for me is my grandfather, Dr. Joseph Jones, who fought a battle for preventive medicine for people in Louisiana during the last quarter of the 19th century—a period known as the "reconstruction period" in the South, but which we now see was a constructive period for the whole country, particularly in preventive medicine and public health and in the developing functions of hospitals. Following in successions of privileged associations for me were General William C. Gorgas, Dr. William H. Welch, Dr. Hans Zinsser, Dr. C. E. A. Winslow, Dr. Thomas Parran, Dr. Milton C. Winternitz, and many others, coming to the time of the last war when I served in the Preventive Medicine Service of the Office of the Surgeon General of the Army, under my former chief, Brigadier General James S. Simmons, who held the honor of the Bruce Lectureship last year.

To these personal associations you have added for me a memorial link with the life and work of Dr. James Deacon Bruce. While I suspect that if he were living he would not agree with some of the things I shall say today, I feel that he would approve of my topic of the hospital as a center of preventive medicine. Dr. Bruce understood clearly the functions of hospitals

* The James D. Bruce Memorial Lecture on Preventive Medicine for the year 1949, delivered at the Thirtieth Annual Session of the American College of Physicians, New York, N. Y., March 28, 1949.

as centers of education and health service. He recognized that hospitals are social institutions. He devoted his good life to the persuasion of men to work together toward an ideal of improvement of the quality of medical care, and his ideas about good medical care included a broad conception of preventive medicine.

I refer to the lifetime of Dr. Bruce, from his birth in 1872 to his death in 1946, not only in a memorial mood, but also to personalize and bring close to us the three quarters of a century that contained the historical settings and sequence of spiritual, intellectual, economic, social and scientific changes that determined the conditions of today and provide material for the future. Enormous industrial development, increased concentrations in cities, and admission of millions of poor immigrants followed soon after the unification of the United States was assured by the Northern victory in the Civil War in 1865. Wars, the product of social unrest and the instruments of social change, were important in this period. When Dr. Bruce was born in 1872, the Franco-Prussian War had but recently ended and Bismarck was turning to the development of national health insurance in Germany. The losses from typhoid fever in the Spanish-American War in 1898 forced attention to preventive measures and at the same time furnished the opportunities that led to the control of yellow fever. The whole public health movement in the United States went forward. The first World War, in which Dr. Bruce served, was a vigorous training period for epidemiologists and preventive medicine officers, and in the second World War new powers over infectious diseases, a vast range of casualties and hazards, and over emotional disorders were developed.

The first quarter century of Dr. Bruce's life, from 1872 to 1900, was the heyday of discovery of the bacterial causes of disease. On the basis of the discoveries of Pasteur, Koch and many others, which established germs in place of devils as the causes of pestilences, there arose a sense of man's liberation from superstition. Preventive medicine developed rapidly as a discipline of elimination of single causes of disease. Beneficial as this was, and greatly as it contributed to successful mass actions of public health and to individual protection, it retarded progress by being too narrow. Ideas of single etiologies delayed recognition of the fact that disease may be regarded as an "entity" only for convenience, whereas in fact the causes are multiple and disease is a group of conditions in a total person in an environment.

The application of these bacteriological discoveries had a tremendous effect upon hospitals. It annihilated fatal "hospitalism" and made hospitals safe. As Churchill has pointed out "Listerism" increased the demands for hospital care beyond any possible expectations. Hospitals like modern cities now owe a large part of salvation of their size and complexities and abilities to function as centers of health services to applications of public health and preventive medicine. It is but natural that they should be centers of extension of service in those fields, that they may become increasingly houses of prevention instead of houses of pity.

In the same period psychiatry advanced through the work of Freud and others. The Hippocratic concept of psychosomatic medicine was revived with new force. Realizable objectives were seen in the study and management of the emotional components of disorders. It became possible for the hospital to provide for "holistic medicine" by a kind of work long familiar to family doctors, in which consideration was given in the wards and clinics to the total individual and his environmental relations and problems.

Within a few years of the birth of Dr. Bruce the revolution in nursing started by Florence Nightingale was affecting medical care in this country. Schools of nursing were established in New York, New Haven and Boston, initiating the development of modern professional nursing as a powerful component of both remedial and preventive medicine, and public health.

During this period progressive humanitarians in this country attempted, as the Beards have said, "to overcome by public and private collective actions, the poverty, disease, misery and hazards which millions of Americans suffered. It was their thesis that such adversities mocked the liberty, equality, pursuit of happiness, and general welfare professed as American ideals at the establishment of national independence." Notions of the "right to health" became widespread. Whether this "right" is admitted or debated, the social philosophy developed in this period has a strong influence upon the present demands for preventive medicine and health services, centered in hospitals or elsewhere. Such services came to be regarded as essential, and it has been observed that the more essential a service and the means for providing it become to the people as a whole, the more they become involved with government. Through the latter part of his life Dr. Bruce was concerned with the question of equal access of all to comprehensive medical care of high quality, particularly through his interest in child welfare. The questions of today, rising from these social movements, concern in general the whole problem of providing for security in a free enterprise system. They include preventive medicine and the hospital as a center of preventive medicine.

Although definitions have been implied in the foregoing, they should be more specifically stated as premises for the following discussion. The word "hospital" means vastly more than the dictionary records. There are many types of hospitals supported in many different ways—general hospitals, special hospitals, voluntary, municipal, state, federal and military hospitals. Whatever their fields of concern and methods of support all hospitals have the characteristics of being organizations with physical facilities and associated trained staffs for the care of the sick in bed in their in-patient services or on their feet in the out-patient departments. Among their functions are service, education and research. In the social order they belong to their communities.

The term "preventive medicine" is a dialectitian's delight. A review of the definitions that have been given to it would fill a book, and to discuss the connotations of the term would occupy tedious days of exegesis. Some would limit it to individual activities, and assign its practice to the family

doctor, separating preventive medicine from the mass activities of public health. Others, emphasizing the limitation imposed by the adjective and the negativistic connotation would abolish the term and substitute some new word meaning the promotion and fostering of health, or the construction and reconstruction of health. For the purposes of this paper and in accordance with a habit of thought I would define preventive medicine, in the words of General Simmons, as "the sum total of all those services required to prevent disease and keep well people well." This broad conception is expressed also by Smith and Evans in their definition of preventive medicine as "all medicine that seeks to alter the course of disease or to better the patient's physiological status." Preventive medicine in this sense has been called "an alliance with nature to prevent disruptive forces." Furthermore, there is no real dividing line between curative medicine and preventive medicine. It is natural, therefore, that the hospital should be a center of preventive medicine for the extension of medical service and the raising of the health level of the individual.

None of these ideas is new. They have been newly expressed, however, in recent important publications. In 1946, Corwin wrote: "Hospitals and their out-patient departments are increasingly being looked upon as strategic centers for all health service activities." In 1947, the Commission on Hospital Care observed: "The service frontier of the hospital has been extended from the sick person in the hospital bed to the potentially ill person in his normal living. General hospitals are in a unique position to offer a locale from which the campaign for better health can be directed. The hospital can be the medium in many communities through which doctors, nurses and both voluntary and governmental agencies can pool their efforts for improving the health of the people." The report of the New York Academy of Medicine Committee on Medicine and the Changing Order, in 1947, pointed out that "The whole perspective of hospital care should be enlarged to include preventive as well as curative care. If the out-patient departments can be effectively utilized to this end and then integrated with home care, the hospital will begin to realize its potentialities as the natural center for all medical service."

If I may add anything new to the discussion I believe it will be in the presentation of a list of the chief preventive medicine activities which are now carried on either extensively or partially from the hospital as a center, or which might be developed from the potentialities of the hospital as a center of health service. Statements about hospitals as centers of health service have been rather general and I have not found an assembled listing of these activities and possibilities. In offering it I do not wish to imply that it means exclusive centering of these activities in hospitals, but present it as an indication of the specific part that hospitals have to play in the total concern that individuals, practitioners of medicine, lay, governmental and professional organizations—from the simplest to the most complex system—share in fostering health. It seems to me that the best examples of preventive medi-

cine centered in hospitals are those provided by the teams in pediatrics, and in obstetrics and gynecology. Almost all elements are included in their programs.

While divisions of the material are convenient, they are not really natural, because all these activities are integral parts of the whole. Divisional arrangements in fact may do harm by strengthening the existing departmental barriers which present some obstacles to communication and concerted effort. With these reservations, and a frank admission of incompleteness, the following listing, with some comments on requirements, is suggested:

I. General Considerations

1. *Attitude.* There appears to be a wide acceptance among bodies that have studied modern hospitals that the hospital is a social institution with special capacities and obligations to function as a center of medical care, and health services, and that in this conception preventive medicine has an "overall significance." While this is a point of view of some administrators, some medical professional groups and many trustees or responsible officials, it is not universally accepted and is opposed by portions of the medical profession, and by some organized medical associations. It is suggested that more than respectful attention be devoted to it. If that were done, artificial divisions between curative and preventive medicine would disappear, certain services would be strengthened, new services would be developed, relationships would be extended and coördinated and a unified effort would be made in the common purpose of having the hospital participate to the fullest possible extent in contributing to comprehensive medical care.

2. *Facilities, Equipment and Construction.* One of the difficulties in the way of developing hospitals as centers of health services is that they have been built and equipped primarily to take care of sick people in beds within the hospital or in clinics for the ambulatory in their out-patient departments. Not only additions, but construction in accordance with enlarged conceptions will be needed. This construction will involve particularly out-patient departments, doctors' offices, laboratories, accommodations for special services, space for occupational therapy and rehabilitation, more space for all functions of nursing, central offices for a large group of related agencies, interior traffic and external transportation, space and equipment for records and statistical work, accommodations for specialties, more space and equipment for education and research. At present many of these activities and services are crowded, usually without systematic arrangement, into the buildings constructed in accordance with the limited ideas of an era now past. Taking a lesson from this rigid past, it would be well to devise construction and arrangements sufficiently flexible to be adaptable to changes in ideas and activities as they develop in the future.

3. *Education.* All hospitals are inevitably concerned with education through the very nature of their daily services which bring together all sorts of workers, patients, doctors, medical students and nurses. This was recog-

nized by Samuel Bard in this country as early as 1769 and the educational and training programs of hospitals, both those directly connected with medical schools and those without such connections, have steadily increased in general and in specialized fields. There remains, however, to be developed in the hospital greater educational emphasis on preventive medicine, the significance of group practice, education of patients in the carrying out of instructions for their own good, adult education, health education, and educational influence upon curricula of medical schools and resident training through the exhibition of the changing experiences of hospitals, such, for example, as is occurring through increase of types of the diseases characteristic of an aging population. An appreciation of the social science aspects of medicine will bring into the clinics as parts of the medical team psychologists, sociologists, cultural anthropologists, and possibly also economic, legal and religious advisers. Public education in general and along lines of preventive medicine could extend from the hospital in many directions.

4. *Research.* The opportunities for investigations in the whole field of medicine and human biology centered in the hospital are too obvious to require elaboration. There are, however, unrealized possibilities for research in preventive medicine in almost every department of a hospital.

5. *Relationships.* There is no person, group or agency in the community as a whole that may not be related in some manner to the hospital. If these relationships are not cultivated by the hospital they will be imposed. No relationships are more natural or close than those concerned with public health, preventive medicine and general welfare. At present they are increasing with federal, state and municipal health agencies, with regional relationships between hospitals, and with hospital, medical and health insurance plans, whether voluntary or supported by money derived from taxes or imposed contributions. The hospitals have a central position in the current discussions of all systems of medical care. The more these systems provide for comprehensive medical care the more will preventive medicine become important in the hospital's relationships with these plans.

Professional relationships are in the very center of all the internal and external activities of the hospital. Although they present difficult problems, it is to be hoped and expected that each party concerned in these professional relationships will be moved by inclination and demonstrated needs to provide enlarged services of preventive medicine.

Although some details have been included in the list of general functions and considerations, a large number of special activities need to be designated separately. Among these are the following:

II. Special Activities, Facilities and Arrangements

1. Diagnostic clinics, with services available to all persons of all economic levels.

2. Consultation services available to all.

3. Extension of connections with physicians of a community, particularly general practitioners and family doctors.

4. Periodic health examinations for the well, in general diagnostic clinics, or in clinics equipped and oriented for the detection of cancer or other diseases. Early detection of chronic diseases is a new essential for preventive medicine.

5. Child welfare and child development clinics, including nursery schools. For preventive medicine the full development of modern pediatrics is of incalculable importance.

6. Pre-natal clinics and post-natal clinics, maternal welfare, and facilities for advance and application of knowledge of human reproduction, emphasizing preventive medicine. Departments of obstetrics and gynecology have led the advance, but the activities and points of view should be shared by other departments.

7. Preventive dentistry and oral hygiene, with inclusion of modern stomatology, capable of recognizing in oral lesions the superficial and deep evidences of a wide range of diseases.

8. Health services for the institution's personnel and associated staffs and groups.

9. Concern with industrial medicine. This may be developed by examinations of persons sent to the hospital, or by examinations at plants through arrangements with the hospital, by personnel trained not only in general medicine but also in the recognition of industrial hazards.

10. Follow-up clinics, and continuity of care.

11. Treatment and prevention of communicable diseases, by maintenance of service for treatment and education; by immunizations, and by linking the community's programs for control and prevention of tuberculosis and venereal diseases (and other diseases) with the activities of the hospital.

12. Nutritional advice and supervision.

13. Social service departments, enlarged and more integrated into the medical team.

14. Coördination of hospital activities with services of visiting nurses and public health nurses.

15. Development of group practice centered either in the hospital or in relation to medical groups of the community.

16. Development of programs for convalescent care and home care, centered in the hospital, motivated by a sense of continuity of service.

17. Development of record keeping, mortality and morbidity statistics and reports, particularly morbidity reports, to utilize to the full extent the hospital's capacities to serve as a center of epidemiology and control of disease.

It is admitted that this list includes nearly all of the functions of a hospital, and perhaps some not yet undertaken. However true that may be, it was not presented in this manner to stake out an over-ambitious program

for preventive medicine, but to draw attention to the fact that there is an element of preventive medicine in almost every activity of the hospital, and that if hospitals are to fulfill their destinies as centers of health services they will need to strengthen many existing arrangements and develop new ones.

Incomplete as this outline of activities and discussion may be the implications for involvement of the hospital in all the contemporary controversial issues regarding provisions for medical care are plainly apparent. These questions include costs and financial support of hospitals, the preservation of voluntary hospitals, the expanding development of government hospitals, voluntary and governmental medical service plans, the old question recently revived whether a hospital should be limited by law to hotel service and is a reprehensible corporation practicing medicine when it participates directly in a broad plan for medical care. I am glad that my topic today does not require my attempting to answer these questions at this time.

As the list includes a number of activities that are working out satisfactorily in all the relationships of the hospital, it indicates a source of evidence and wisdom that should be utilized as a guide in further developments of relationships between hospitals and physicians and between hospitals and their supporters. Some of these activities are experiments of a type much needed in many differing parts of our country before any single system of medical care and preventive medicine is adopted for the whole people. Perhaps they may afford some preventive political significance along with the benefits of preventive medicine.

In this discussion I have tried to outline an operational plan and some of the logistical aspects of enlarged services of preventive medicine centered in the hospital. As I said at the start I do not know what the founder of this lectureship would think of these ideas if he were living and if we could consult him. However controversial these matters may be, I trust that I have spoken of them in the spirit of Dr. Bruce.

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THE ALLERGY FACTOR IN DISEASE*

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Perhaps I should have chosen to discuss the more practical diagnostic and therapeutic aspects of allergy but I am particularly anxious to present some of the more recent tendencies in our thinking about allergy, particularly the rôle that the allergy concept is playing in Internal Medicine since it seems to concern itself so importantly with the pathogenesis of certain diseases, the etiology of which is at present unknown.

First, we must understand just what we are talking about when we use the word "allergy" or the term "allergic disease" and something of the nature of the reactions we may expect. There is at present no concise and generally accepted definition. Let me explain it this way: disease is a reaction of body cells to an abnormal environment. In general we may say that this is caused by the introduction of toxic substances of any kind including those resulting from bacterial and viral invasions which have a *direct effect* upon various and sundry tissue cells or in some instances it is created by the absence or imbalance of various glandular secretions, in others by too much or too little of the products of nutrition and of normal cell activities. The point is, the reaction is the result of direct action.

Contrariwise there are substances, in themselves usually harmless, which by *indirection* produce profound and even lethal effects upon tissues because of the existence of a specific cellular sensitization, for sensitized cells when combined with an antigen seem to liberate some new active substance or poison and the resulting reaction constitutes allergy. In other words, allergy as I use it includes all manifestations resulting from antigen-sensitized-cell reactions and only these. It is a mediated reaction and if there is no cell sensitization, no antibody as mediator, there is no allergy. Since most of the various tissue cells seem to be capable of retaining or adsorbing antibody if elsewhere produced, thus becoming sensitized, it is easy to appreciate the widespread and protean aspects of an allergic response in the presence of the appropriate antigen or allergen. These latter words may be used synonymously to designate the substance with which the sensitized cell reacts, whether or not it has been the actual generator of the cellular antibody.

But it is necessary to go a step further and appreciate the fact that all antigen-antibody reactions are not identical. The tissue responses vary with the nature of antigen, type of cell or immunologic mechanism involved. The fact is that the reaction is always "altered" from that of the same substance acting on a non-sensitized cell; hence the reason for the adoption of

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From the Allergy Division, Roosevelt Hospital, New York City.

Von Pirquet's term "allergy" to describe all these "altered" cellular reactions.

Let me cite the following examples of at least three different types of allergy.[1] When the patient with a history of typical autumn hay fever walks into a ragweed pollen infested area, the symptoms of hay fever begin within a relatively few minutes. If skin tested, scratch or intradermal, with an extract of ragweed pollen, he develops an urticarial wheal and flare also within a few minutes. His serum will transfer the same prompt reaction to the skin of a normal man. These reactions, both clinically and by test, are immediate and urticarial or edematous in type and, as was said, are transferable because there is antibody free in the serum (humoral) while only that bound to the cells (somatic) of the patient accounts for the reaction. This first type is spoken of as the *"immediate allergy,"* for both clinically and by test the response is immediate and the test reproduces the tissue change characteristic of the disease. This is typical of the allergy to air-borne allergens as pollens, danders and dusts causing coryza and asthma. It is also encountered in certain food allergies especially in infants and occurs in patients after anti-sera, insulin and other biologicals.

Now for an example of a second type. Everyone is familiar with the positive tuberculin test. This is a *"delayed reaction"* appearing not immediately but in 24 to 48 hours, inflammatory in character, obtained by either patch or intradermal test with tuberculin. It occurs only in those who have been infected, that is, have had prior contact with the tubercle bacillus as a result of which they became sensitized to tuberculin. That this is a transferable reaction has been definitely proved by Chase.[2] By the use of massive doses of killed tubercle bacilli and adjuvant injected intraperitoneally into guinea pigs, an allergy to tuberculin was stimulated without active infection. By injecting washed cells of the peritoneal exudate, the reticulo-endothelium, or spleen and lymph glands from the tuberculin reacting animals, he transferred to nontuberculous animals a skin sensitivity to tuberculin whereas the serum of these same animals did not effect this result. In other words, the existence of a mechanism that is strictly cellular and not humoral was shown. This is allergy as it is an antigen-antibody cell reaction and again the test closely simulates the histo-pathology of the disease as stated by Sabin and Joyner.[3] Evidence that a systemic tuberculin sensitivity can be passively transferred has been presented more recently by Kirchheimer et al.[4]

Our next type is the "dermatitic" and an example is that of a patient presenting himself with an itching vesicular rash, especially on exposed parts of the body. The story is that one or two days before his symptoms occurred he went for a stroll in the country. We diagnose it dermatitis venenata and if correct it can be shown—this time by a patch test with an alcoholic extract of poison ivy to the skin surface, not a scratch or intradermal test. When the patch is removed at 48 hours there is a typical exudative dermatitis at the test site. Again, the test is a duplication of the clinical lesion. This reaction is delayed like that to tuberculin yet is not histolog-

ically identical. It is an allergy in which sensitization resulted from some earlier contact. The evidence is that babies and Eskimos never having had any contact do not react to poison ivy at first. It has no escharotic action, but a few weeks later 75 per cent of the infants will give a delayed reaction on patch test after having had no more contact than the one non-reacting test.[5] The point is, the reaction is "delayed" not immediate; it is an exudative inflammation not an urticarial wheal; and antibody does not exist in the serum and hence passive transfer of sensitivity by serum is impossible. Using the technic of Chase, this dermatitic reaction to poison ivy has been successfully transferred in guinea pigs by Crepea [6] in our laboratory at Roosevelt Hospital by the injection of lymphoid cells from a sensitized to a non-sensitive animal.

To give a picture of these several variations of the reactions included under the term allergy, I have attempted a classification [7] or frame work which is not entirely adequate, is probably temporary or will need amending as knowledge expands, but it serves to indicate what I particularly wish to stress and that is the basic differences that apparently exist in the mechanisms of the cellular reactions which are included under the heading of allergy.

Now a word about antibodies. To know what they are and whence they come and what they do is naturally of paramount importance. I shall mention only briefly a few of the high lights contributed by many workers. That many antibodies are in the globulins, especially gamma globulin, seems now established through the work of Heidelberger [8, 9] and his associates, and of Tiselius and Kabat [10] using chemical and physical (ultracentrifugal and electrophoretic) methods. But actually there is much that is not known and I shall not elaborate on the theories of their formation and specificity as presented by Breinl and Haurowitz,[11] by Mudd [12] and by Pauling,[13] nor on the chemical and immunologic relationship of enzyme and antibody as presented by Sevag.[14]

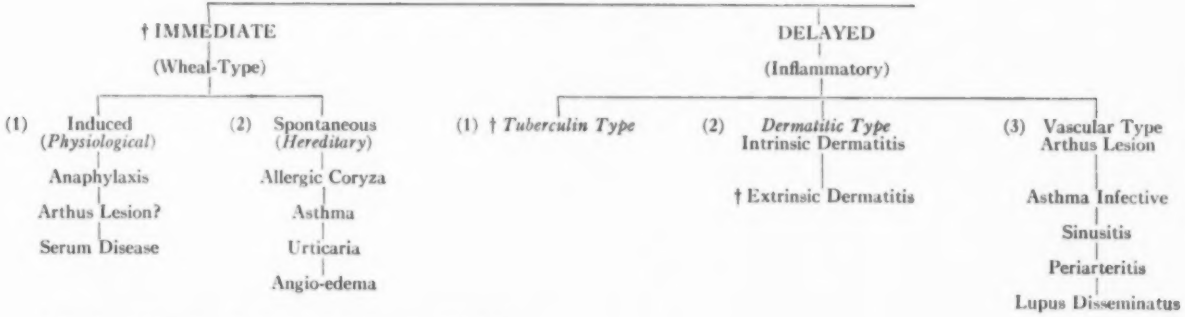
It is interesting that the reticulo-endothelial system, as long ago suggested, was shown to be a site for antibody formation by Sabin [15] through the ingenious use of a dye-protein antigen. The lymph nodes (lymphocytes) are also included in those tissues contributing to antibody production.[16, 17] There is at present no proof that other types of cells have this capacity though Ehrich and Harris [18] believe the granulocyte and microphage may play an essential rôle. The release of gamma globulin to the blood under control of the pituitary adreno-cortical hormone as presented by White and Dougherty [19, 20] indicates the intricacies of antibody control. All such searching studies that have been going on over the recent years have much to do with allergy because they concern the basic mechanism of allergy.

Antibodies are stimulated by contact of the cells with antigens and their presence may be beneficial and afford protection as antitoxins or they may be a liability to the host as in the case of allergy. As far as is known, the antibodies of allergic reactions are somatic, that is, are attached to the living

TABLE I

Allergy*

(Antigen-Sensitized Cell Reactions)



* Reprinted from Am. Jr. Med. (1947, iii, pages 523–534).
† Antibody mechanism has been demonstrated.

tissue cells of the host. But there are many other antibodies which are humoral, have no somatic attachment, and have immunologic and diagnostic significance only like agglutinins and precipitins (Widal reaction), or a protective value as antitoxins, yet their presence has no known bearing on the production of disease symptoms or lesions. This concise statement is an over-simplification of an intricate problem and there is still great need for a continuing study and clarification of the idea that sensitizing (allergic) and protective (immune) antibodies are not the same, a thought supported by Rich [21] in his studies on tuberculosis and illustrated by the blocking antibody found in the sera of treated hay fever patients by Cooke et al.[22]

When antigen unites with antibody in the sensitized cell, an allergic reaction occurs, immediate or delayed as the case may be. What happens and why? This is the crux, what is popularly known as the $64 question. Much thought and study have gone into the attempts to answer it. In the early work on anaphylaxis one striking feature of the reaction was that no matter what the antigen, the symptoms in any one species were identical. This led to the search for a so-called anaphylatoxin which was liberated from the reacting cells. Following the extraction of histamine from ergot, Dale and Laidlaw [23] noted that its pharmacologic effects on animals resembled anaphylactic shock. In the Herter Lectures of 1919, Dale [24] stated that since histamine is present in normal tissues and because of its pharmacologic action and potency, "the suggestion lay near at hand that the long-sought active substance was 'histamine' and that the production of the latter in the system was the cause of anaphylactic shock."

We had come to think until recently that with the histamine discovery, anaphylaxis was practically a closed chapter. Histamine contracted bronchial smooth muscle which caused obstruction and death by asphyxia in the guinea pig. But the atomic age has provided new technics and by the use of radioactive iodized tracer antigen, Warren and Dixon [25] appear to have shown that bronchial edema not muscular constriction is the most important factor in bronchial obstruction. This does not controvert the histamine theory, for histamine also produces edema, but it does alter our ideas of the pathologic physiology of anaphylaxis. While there are still some discrepancies to iron out, there is today a fairly general consensus that histamine is one of the factors both in anaphylaxis and in allergies of the immediate wheal type.

It certainly does not appear to me that this explanation can be made to or will apply to the delayed allergies of the tuberculin or dermatitic types for these reactions bear no resemblance clinically, pharmacologically, histologically or immunologically to the prompt effects which histamine is known to produce. That other agents may exist pre-formed or are produced in the cells in these delayed allergies seems highly probable; in fact, this is quite in line with the ideas and findings of Menkin [26] who has isolated various (toxic) substances from inflammatory exudates; for example, leukotaxine, pyrexin, necrosin and others, each producing its own special effect. There is as yet

no answer. But it is on account of the histamine liberation in the immediate wheal-type allergies that a new class of drugs known as anti-histaminics has been developed and about which I shall speak briefly later on.

It is not disparaging of the clinicians who practice in whole or in part in the field of allergic diseases to state that the most important advances and greatest contributions to our knowledge of allergy in recent years have come from investigations in the basic science fields of physiology and pharmacology, pathology and physics, chemistry and immunology. As a result of these contributions, applied allergy has been forced to broaden its view from the narrow confines of such accepted diseases as hay fever, asthma, eczema and urticaria and serum disease which over the past few decades were made susceptible to diagnosis, and often a mistaken one, by the simple technical procedures of skin testing and to therapy by the empirically graduated injections of the reacting allergens.

Today the principles of the allergic response are being invoked in the hope of explaining the pathogenesis of important diseases * of man which lie entirely outside the present scope and the practice of the so-called allergist. Among these may be mentioned rheumatic fever and rheumatoid arthritis, periarteritis nodosa, Loeffler's pneumonia, lupus erythematosus, scleroderma, sarcoid, eosinophilic granuloma, glomerulonephritis, certain encephalopathies and multiple sclerosis, the entire erythema group and purpuras, erythroblastosis fetalis, paroxysmal hemoglobinuria, leukopenia, hemolytic anemia and hemolytic activity of incompatible bloods, sympathetic ophthalmia and other ocular lesions involving the conjunctiva, sclera, cornea and uveal tract. Allergy is likewise invoked to explain the histopathology of certain diseases of known origin as syphilis, tuberculosis, tularemia, sporotrichosis and coccidioidomycosis, brucellosis and the rash of scarlet fever. It is the basis for diagnostic tests of the tuberculin type not only in tuberculosis but in typhoid fever, brucellosis, lymphogranulomatosis, fungus diseases and others. In such ways then the principles of allergy are being applied broadly but most importantly to a study of the pathogenesis of diseases of unknown cause. It provides a new angle of attack.

Two of the more important clinical fields in which interest has developed are those of bacterial allergy and drug allergy.

Bacterial Allergy

That there may exist a peculiar and specific sensitivity, what we now call allergy, to bacteria or their products has long been known, for Koch (1889) reported that the reaction, both locally and systemically, to his tuberculin was a specific response obtained only in tuberculous animals. It is not profitable here to venture exhaustively into the story of the gradual development of our present ideas of bacterial allergy but I shall merely state some of

* Some of the more important contributions on these diseases are included in references 27 to 55. Many of these references have been selected on the grounds that they give an up-to-date bibliography.

the principles and interpretations as we now see them in order to elaborate on certain practical applications.

Bearing in mind what was said earlier on types of allergic response, bacterial products may be concerned in (1) the immediate wheal-type reaction; (2) the tuberculin type; (3) the dermatitic type and probably also in the visceral and vascular lesions about which we still know relatively little immunologically speaking save that they appear to exist. While bacterial products in themselves may be the antigens they also act as synergists or adjuvants in the production of antibody even to homologous cells—so-called auto-antigens—as in the experimental studies of Kabat, Morgan, Cavelti and others in multiple sclerosis and glomerulonephritis.

Immediate Wheal-Type Reactions: By using bacterial proteins it is possible to produce a typical anaphylactic reaction in the experimental animal as was done by Rosenau and Anderson in their classical studies in 1907. In various diseases of man whether due to a bacterium, fungus, or to metazoan or protozoan infestations, examples of this immediate and specific wheal reaction are recognized and in some few instances have acquired diagnostic value. It is well known that the polysaccharide fraction of the pneumococcus and meningococcus gives a type specific wheal reaction in the skin of patients in the later stages of the disease and its presence indicates a favorable prognosis in pneumonia patients, according to Francis.[56] Occasionally one may secure immediate wheal reactions and immediate systemic reactions to the fungus extracts, oidiomycin and tricophytin, to the toxins of diphtheria and tetanus and to specific extracts after infestations with such parasites as echinococcus, trichinella, filaria and schistosoma. In general, one may say that there is little pathologic, symptomatologic or important diagnostic significance to this immediate wheal-type bacterial allergy in man.

The Tuberculin Type of Allergy: The delayed inflammatory and specific reaction to infection tells a different story. Based upon the extensive experience with the tuberculin test, a reaction indicates allergy. It must always put the physician on guard to determine by all possible means whether the infection exists and is responsible for the patient's symptoms or is merely the remains of past and conquered disease. As a result of his careful work with tuberculosis and syphilis, Rich [57] is led to the opinion which he expresses thus: "In a very realistic sense it may be said that the presence of allergy converts, in effect, a bacterium which does not produce a toxin into one that does, i.e., it converts a harmless protein product of bacterial disintegration into a violent and even lethal poison."

The tuberculin-type allergy may exist to any invasive organism of man and once an infection has taken place the allergy may persist for years or through life even though the infection be cured. For this reason specific tests are useful in diagnosis only under special conditions and in certain diseases such as tuberculosis, typhoid fever, brucellosis, tularemia, dermatophytosis, lymphogranulomatosis and others, but in any and all cases a positive test does not indicate an existing active disease and careful clinical and diag-

nostic acumen is required in the interpretation. The same must be said for tests with all bacterial vaccines and products of such common organisms as the staphylococcus, streptococcus, pneumococcus and others.

But there is a very special and practical reason in my mind for this brief survey of the basis for bacterial allergy. Reference was made earlier to the possibility of allergy in such typical infectious diseases as rheumatic fever, tuberculosis and syphilis. Rheumatic fever is a disease of varied pathologies, involving joints, nerves, muscles and viscera. Swift and his associates [58, 59] have supported the bacterial allergy theory on the basis of clinical and experimental evidence. They found that a focus of bacterial substance was necessary to the primary development of an allergic state which then could be maintained by re-injection of the specific vaccine whereas such vaccine injections had no effect on the non-allergic rabbits they used as test animals. To this crucial point I shall allude later. Another significant finding from these rheumatic fever studies was that there was no one specific organism nor strain of organisms that played the etiologic rôle, though certain strains were more active than others. The allergy theory explains how many different organisms and types of streptococci produce the same clinical and pathologic picture, a feature that is very typical of allergic disease.

Rich [60] has accepted the allergic basis from the anatomic-pathologic point of view on account of the resemblance of rheumatic fever lesions to those he finds in patients after allergic reactions to serum or drugs, namely Aschoff bodies, focal lesions of heart muscle and valves, fibrinoid degeneration of collagenous tissue and blood eosinophilia.

Infective Asthma: Now to be more pointed, what can be said about therapy in cases of asthma based solely on infection, cases in which foods and air borne substances play no or a minor etiologic rôle? In the first place, many different types and strains of bacteria produce the typical signs and symptoms of asthma when the shock organ or sensitized tissue comprises components of the bronchial tree, especially the mucous membrane and submucosa. For this statement substantiation is found in the fact that minimal subcutaneous doses of a proper bacterial suspension will produce a symptomatic response, namely asthma. This is analogous to the focal reaction in tuberculosis following a tuberculin injection for diagnosis or treatment. Secondly, the pathologic picture of fibrinoid degeneration of tissue as well as eosinophilia in the bronchial walls and blood tends to support the hypothesis of allergy. Finally the factor of focal infection, so necessary to the development of a bacterial allergy in experimental animals as found by Swift in his rheumatic fever studies, is discoverable in 90 per cent of the patients with asthma beginning after the fortieth year of age, but often in earlier life.

This question of infective asthma has interested us at the Roosevelt Hospital for many years and an analysis of the data at hand supports this allergic hypothesis. But now let me be a little more specific and practical. Mention was made of the focal infections needed to develop an allergy and found in such a high percentage of cases. The primary foci lie in the upper respira-

tory and oral tracts—that is, sinuses, tonsils, lymphoid tissues of the pharynx and teeth. Evidence that such foci antedate the asthma may be established by a careful history, or in those patients seen early in their asthmatic career, by the fact that the degree of the tissue change in the focal areas indicates its prior existence and chronicity. Further, in many patients with allergic coryza with or without asthma of an environmental (air borne) etiology but in whom examination established the presence of definite, let us say, sinus disease, I have witnessed with the passage of years the gradual development of a typical infective and allergic asthma. This is illustrated by the following case summary:

In 1940 I saw a patient, then aged 48 years. His chief complaint was urticaria of six months' duration. A physical examination at that time revealed the presence of extensive hyperplastic sinusitis involving both antra. The urticaria of unproved etiology gradually cleared and the patient was not seen again until 1947 when he returned on account of a continuous and severe asthma of six months' duration. Two years prior to this he had developed diabetes, requiring insulin therapy. No cause other than infection was found to explain the existing asthma. The gradual improvement which began after sinus surgery at this time (1947), and has continued to date, supports the etiological significance of the primary antral infection and an asthmatic reaction after injections of autogenous vaccine made from antral tissue cultures indicates its allergic nature.

From these comments you may correctly conclude that I disagree with the ideas so often advanced that the hyperplastic changes in the sinuses and bronchi are concomitant manifestations of some mystical and unknown common factor causing both asthma and sinusitis. The mystery mainly is why certain infections give rise to hyperplastic sinusitis in some and not in others and why many such persons eventually become asthmatic.

The practical aspect of this concept leads straight to these conclusions: all patients with asthma, and especially those with asthma beginning after about 40 years of age, should be carefully studied for areas of focal infection and this should be done as soon as asthma appears or earlier if the patient is examined for other allergic symptoms. This step should not be postponed while pursuing years of fruitless symptomatic therapy. Once asthma begins it may subside but practically always returns with increasing intensity and continuity since the cause, that is the primary focus, is allowed to persist. Drugs and climate at best only retard the progression. An etiologic diagnosis and therapy directed against the cause should be undertaken promptly and not after years of incapacitation and physical exhaustion as happens much too often in such cases.

The same may be said for those patients, often much younger, with seasonal or perennial coryza from any cause and those allergically predisposed with frequently recurring bronchitis. In addition to the continued treatment with pollens or dust extracts as etiological factors, a search for focal infection should always be made regardless of whether the patients have asthma

or not. If suggestive evidence of a focus is found, the patient should be watched periodically for an extension of the lesion or increase in symptoms. Assuming one has found such a focus, the question is what can be done about it. If the allergic symptoms are recent, mild and intermittent, one is justified in temporizing. But if the focus such as an antral cyst or polyp persists, even though asthma has disappeared for the time being, the question of its removal must be carefully weighed. The only adequate measure today for a chronic infective focus is its removal by surgical procedure for there is still no other remedy even including adequate and prolonged penicillin or other antibiotic therapy by any parenteral route or by aerosol inhalation. In our hands at the Roosevelt Hospital these latter measures have been temporarily helpful but as a rule not lasting.

I realize that there is still considerable opposition to surgical procedures, particularly as far as sinuses are concerned, on the ground that the results have not been good. My answer is that the steps taken are too little or too late, and if there be fault, it lies equally with the internist or allergist and the rhinologist in failing to realize what may be accomplished in cases of infective asthma by early and adequate surgery. In the most recent review of several hundred patients with cases of asthma operated upon by Grove [61] at our clinic since 1932 and in which all indicated surgery had been carefully done, there was substantial improvement in over 75 per cent. A further breakdown of these figures reveals that in this group 30 per cent were free of asthma for from two to 14 years after operation and of these nearly 60 per cent had had asthma less than five years. Such figures indicate that the earlier the removal of foci the more satisfactory the results will be.

This is not to be interpreted to mean that surgery must continue indefinitely to be our main reliance instead of a last resort. To me the proper conclusion is that we must learn how to prevent focal infections which are important not alone in asthma and other allergies, but also in many diseases involving all tissues of all the systems of the body. Dental prophylaxis as witnessed by the work on the prevention of decay is now coming to fruition. Should we as physicians do less toward the prevention of sinus and tonsillar disease, those areas of infection which are the primary focal seat in a vast majority of cases? This is a large order to which too little thought has yet been given. The basic causes of susceptibility to infectious disease in man have as yet received scant attention.

Drug Allergy: Untoward reactions to drugs [62] are so common they are met with by clinicians in all fields of medicine, especially since the introduction of the antibiotics. Some of these drug reactions may be a mere exaggeration of the normal actions but many others are unrelated to the usual pharmacologic effects and are regarded as definite or probable allergies. The criteria for allergy are:

1. A history of prior and adequate contact to afford opportunity for sensitization.

2. A symptomatology characteristic of one or another of the allergic dis-

eases as urticaria, dermatitis, asthma, rhinitis together with those symptoms of serum diseases—as fever, lymphadenopathy, arthralgia or skin lesions of various sorts as purpura, diffuse nodular or bullous erythema often pruritic in nature, blood changes as leukopenia and agranulocytosis and possibly hepatitis.

3. A blood eosinophilia.

4. The demonstration of an antibody mechanism by direct or passive transfer skin tests. If present this would be accepted as positive proof of allergy, but such specific reactions are rarely obtained except with drugs or biologicals of protein nature.

5. Finally, a personal or family history of allergy lends some weight to any hypothesis of sensitization in the presence of unusual signs and symptoms though it cannot be counted on as a frequent finding in drug allergy.

Practically speaking, all drugs including biological products and gums are potential allergens but the frequency of sensitization depends on the nature of the drug itself, presumably the constitutional make-up of the patient and also on the method of contact. Sulzberger et al.[93] showed that using four sulfonamides locally applied to the skin for two weeks the average dermatitic sensitization was 23 per cent in 254 cases, whereas after oral administration the percentage of sensitization is about 5 per cent. However, once sensitization is established, a reaction may be elicited by either internal or external contact.

In the pre-penicillin days the reactions to the sulfonamide group were a source of constant worry on account of the frequency and serious character of many of the reactions, notably the vascular lesions described by Rich. Fortunately, the allergic reactions to penicillin, while just as varied as those to the sulfonamide group, are neither so common nor so serious and are often transient in character.

The diagnosis of drug allergy usually must rest upon the simple clinical grounds. In the case of protein drugs and excipient gums an immediate urticarial reaction may be obtained by scratch or intradermal skin test, especially if there are prompt symptoms of the edema-hyperemic type as asthma, rhinitis and urticaria. When there is clinical evidence of dermatitis, a patch test may likewise be positive but in practically all cases of a suspected reaction to crystalloid drugs diagnostic tests generally fail and immunologic evidence for allergy is not obtained. But having regard for the criteria for drug allergy previously stated, the clinical diagnosis in the presence of new and suggestive symptoms depends upon a proper appreciation of the varied lesions and symptoms of drug allergy, a knowledge of previous contact with a drug with or without a sensitivity reaction or its continuous use over a period of one or two weeks which is adequate for the creation of an allergy to that particular drug, at least temporarily. Cessation of the drug usually brings a prompt amelioration of symptoms such as fever, and a renewal of therapy usually induces a prompt return of the symptoms. In those cases in which consideration must be given to the use of a drug that is a suspected

or even proved allergen, resort may be had to small and carefully graduated doses to determine a persistent allergy. A loss of sensitivity to certain drugs as nirvanol, arsenicals and sulfonamides is rare, whereas a loss of sensitivity to penicillin is not uncommon. Resort to the technics of specific immunization, hypo-sensitization or desensitization is practically futile when drug allergies are involved and alternative agents must be used.

Histamine and Histamine Antagonists: As opposed to allergy to drugs it seems appropriate here to discuss briefly that relatively new class of synthetics known as anti-histaminics. There is today substantial agreement that histamine is released within the sensitized cell upon contact with antigen and is therefore responsible for the certain but not all of the evidences and symptoms of anaphylaxis. As said earlier, on account of its pharmacologic action histamine also seems to be released in the sensitized cell in those allergies of the immediate wheal-type as exemplified by the vasomotor rhinitis of hay fever and similar types of urticaria and asthma. Pharmacologically speaking, epinephrine is the ideal antagonist to histamine. As Gilman [64] puts it "both drugs are acting on effector cells in opposite directions and the effect of one tends to neutralize that of the other." The anti-histaminic drugs so-called are blocking agents that are quite specific for histamine. Acetylcholine contracts smooth muscle. The effect is blocked by atropine but not by the anti-histaminic drugs. Contrariwise, histamine contraction is not blocked by atropine but is effectively blocked by anti-histaminics.

As a class these anti-histaminic drugs have the effect of inhibiting the whealing effect, that is the capillary permeability of the allergic reaction and the smooth muscle contraction of experimental anaphylaxis. Also they have local anesthetic and sedative actions. The latter, which are extremely variable in man, constitute the main cause of the limitation of their use.

There are a great many of these drugs now available but those mostly in use are neo-antergan, pyribenzamine, benadryl, antistine, thenylene and histadyl, thephorin, neo-hetramine and phenergan. In practice they are solely palliative, are not cumulative, have no notable persistent effect but tolerance is developed after long use. Toxic effects as excitation, depression, collapse, nausea, diarrhea, headaches and dysuria have been noted but vary greatly with the different drugs in different patients. Allergies to these drugs have been reported. In our clinic an urticaria and asthma from pyribenzamine tablets were found due to the gum excipient used and in this case the pyribenzamine did not control the urticaria or the asthma. Recently we have seen two cases of dermatitis produced by pyribenzamine cream locally applied to a pruritic lesion. In such cases the drug does not exert any anti-histaminic action.

The anti-histaminics find their greatest use in vasomotor rhinitis both seasonal and perennial, in urticaria, dermographism and cold allergy. They are of relatively little use in asthma, hyperplastic rhinitis and dermatitis though they do tend to control pruritus through the sedative and anesthetic action. In short, these drugs, in adult doses of 25 to 50 mg. several times

daily as needed, are a useful addition in the therapy of certain allergic symptoms but due to the temporary effects, the depressing action and toxicity, they cannot in present form at least supplant proper allergic management and immunizing therapy except in certain mild cases.

I have endeavored to present to you the meaning of allergy as we know it today, its intricacies, its variations and its range. It is not a single disease but comprises a variety of biologic and immunologic reactions, an appreciation of which has brought about their useful application in an attempt to explain many symptom-complexes that have long been recognized but the pathogenesis and ultimate etiology of which have not been understood. These include diseases not only of interest to the student of allergy but to those engaged in all specialty fields, including most prominently Internal Medicine and Pediatrics.

These possibilities in the development of allergy and its importance in general medicine were definitely foreseen when the question of certification in allergy was under consideration and it was for this very reason that the American Board of Internal Medicine, and more recently that of Pediatrics, recognized the need of extended study and experience in clinical and scientific medicine; hence certification in Internal Medicine or Pediatrics was made a pre-requisite to certification in the more restricted and truly subspecialty field of allergy which is an integral part of them.

Allergy as perhaps no other field today requires men well trained in the medical sciences in order to grasp and to promote an advancement in the concepts of allergy and their applicability to the solution of the problems in the science and practice of medicine. It should be, as I know it is, a matter of gratification to the Fellows and Members that the American College of Physicians was in the forefront of medical organizations to foster and stimulate the greater desire for voluntary and extended study and knowledge of medicine which has been accomplished through the simple expedient of recognition attained through certification.

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RESEARCH PROBLEMS IN CORONARY HEART DISEASE *

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Researches in coronary heart disease until very recently have been largely in the fields of statistical incidence, pathology, diagnosis, prognosis, and empiric therapy. Now and then there have been in the past flashes of interest in the etiology and pathogenesis stimulated on occasion by observations and questioning of a few far-sighted persons like Timothy Leary of Boston, but in general an attitude of fatalism, indifference, or hopelessness has held in check the curiosity of the medical world. "It is God's will" has been more or less the unspoken attitude of both laymen and doctors ever since the first description of a possible relationship between coronary sclerosis and obstruction on the one hand and symptoms and death on the other as recorded about 250 years ago by Theophilus Bonetus and his contemporaries. It is, however, perfectly clear to us now that we must assume something better than a passive attitude towards the increasing threat to the activities and lives of many young and middle-aged persons which results from the development of serious coronary atherosclerosis. It is about this field, namely of etiology and pathogenesis, that we shall speak this afternoon.

Vague ideas and theories and a few scattered observations are all that we can show for our labors to date. Nevertheless, there is beginning to be a keen interest in digging into the problem which has attracted more and more of us in the clinical field during the last decade. Hence what we can present to you today is largely the listing of questions for the future to solve. We have very few answers to date. It is, however, encouraging that we have at least reached the point of recognizing the challenge and of knowing some of the things that we don't know and must learn about. Grants for cardiovascular research, fellowships, and construction of laboratory facilities should have as their first priority the field of etiology. Naturally we must also continue to help the victims of heart disease by improvement in diagnostic procedures, better information about prognosis, and the most expert medical and surgical therapy, but these all pale in significance when compared to the vital studies that loom up in etiology and pathogenesis.

A few years ago I delivered an address in Chicago entitled "The Reversibility of Heart Disease" based on a personal experience over a period of 25 years of such reversibility in every single type of heart disease, including spontaneous recovery (as in coronary heart disease, for example, often poorly recognized) as well as actual curability, medical or surgical. This had been

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an exciting experience, worthwhile and really momentous, but, although such work must be fostered and developed still further, how secondary in importance it is after all in comparison with a full scale attack on the underlying causes of heart disease, which is certain to lead in time to their prevention or at least to their postponement beyond youth and middle age! A quotation from an address given by Oliver Wendell Holmes in Boston in 1860 is appropriate at this point:

"What makes the Healing Art divine?
The bitter drug we buy and sell,
The brands that scorch, the blades that shine,
The scars we leave, the 'cures' we tell?

"Are these thy glories, holiest Art,—
The trophies that adorn thee best,—
Or but thy triumph's meanest part,—
Where mortal weakness stands confessed?

"And lo! The starry folds reveal
The blazoned truth we hold so dear:
To guard is better than to heal,—
The shield is nobler than the spear."

What are some of the fundamental problems concerning coronary heart disease and what do we know about them? Even the questions that we shall present to you are incomplete. Doubtless some of you will have other suggestions as to problems to work on, for the field is tremendous and the harvest in time will be rich. If enough individuals, well trained in the fields of genetics, anthropology, biochemistry, physiology, pharmacology, and clinical medicine work hard enough in coöperative groups during the next decade we are sure that we shall begin to have some important answers and the vision of something ahead that will be well worth our while.

We shall take up now under various headings the essential problems about etiology and pathogenesis of coronary heart disease.

Anatomically we would like to know about the family coronary tree. Is there a family topography of the coronary circulation? What is its adequacy or inadequacy as inherited? Secondly, what is the extent and effectiveness of the potential coronary collateral circulation? We have the foggiest ideas about both these points. There is very likely to be found a considerable individual variation. Thirdly, it has been reported that the coronary artery wall in the male infant is much thicker than that in the female. If this is clearly substantiated, is it one of the reasons for the greater incidence of early coronary artery sclerosis in the male as contrasted with the female? What is the function of the muculature of the coronary artery wall? What functional possibilities are there from varying muscle content in relation to other tissues such as the elastic structure of the wall—this in contrast to the aortic wall on the one hand and the wall of the peripheral arteries on the other? What rôle do the vasa vasorum in their distribution and disease

conditions play in the etiology of coronary atherosclerosis? What is the anatomical distribution of nerves to the coronary circulation, particularly from the standpoint of general or localized vasoconstriction or vasodilatation? Certainly all these are fundamental questions for which we still lack adequate answers.

The second etiological category includes physiological questions which still await answers. What variations are recognizable in the caliber of the coronary arteries both in general and locally? In the case of variations in caliber, which might include spasm with complete temporary obstruction, what rôle do the nerves play in contrast to direct action of chemicals in the blood? Secondly, it is thought that the level of the diastolic pressure is of considerable importance in maintaining the coronary circulation. Is there a beneficial effect, other things being equal, of a relatively high diastolic level in coronary heart disease? May a low diastolic level, as with aortic regurgitation alone, account for clinically important coronary insufficiency, as we think likely? Thirdly, what is the effect of posture or of dilatation of the blood vessels in the legs and splanchnic area on the coronary circulation per se in health and in disease? Is it in cases with marked dilatation of the vessels in these regions who have also coronary insufficiency that benefit may come by the application of an abdominal belt as recommended by Dr. Kerr? Fourthly, is there an optimal heart rate for the coronary circulation? What advantages or disadvantages may there be in various individuals whose heart rates are slower or faster than the usual? Is there ever a reflex change of heart rate and of blood pressure in coronary insufficiency to suit?

The third main category includes pharmacology and, incidentally, treatment. Do the nitrites act beneficially in the main because of general vasodilatation with a drop in blood pressure or is there a preponderant or at least strikingly important effect also on the coronary vessels per se to account for this benefit? Or is there some other helpful effect? Just how much help should we expect routinely or in specific instances from the use of vasodilating or relaxing preparations such as theophylline and papaverine? Of how much value is oxygen inhalation in improving the oxygenation of the blood in the coronary arteries and utilization thereof? Does morphine given for pain in acute myocardial infarction have any important specific effect clinically on the coronary circulation per se? Does digitalis have a harmful effect in altering the caliber of the coronary circulation or in increasing the thrombotic tendency of the blood about which there has been considerable argument? Our present experience, although still not adequate, suggests that there is no important harmful effect from that drug on the coronary circulation per se. But may not digitalis in some instances, through its tonic effect on the myocardium, increase the activity of the heart sufficiently to induce a relative coronary insufficiency when there is limited blood supply through the coronary circulation? Quinidine has apparently acted favorably in some cases of coronary insufficiency. Is this in part due to the clearing up of bothersome and painful disturbances of rhythm in patients with coro-

nary insufficiency or does it have a specific effect on the coronary circulation? Is testosterone a vasodilator of the coronary circulation or does it act in some cases simply by improving general health or by psychotherapy? Similarly, what direct beneficial effects, if any, have the vitamins and hydrotherapy? Finally, certain preparations have been thought to be helpful in preventing or retarding the progress of coronary atherosclerosis, in particular iodides, thyroid extract, and perhaps choline. How much can we expect from these preparations in the future?

In the field of pathology there are a number of questions as yet not clearly answered. In the first place, is atheroma always one process or are there variations of it? Is the harm due largely to the accumulation or deposition of cholesterol in larger and larger amounts or is there, more importantly, an inflammatory and fibrotic reaction to these substances or other substances acting as foreign bodies? What are the incidence and importance of intimal hemorrhages in the production of coronary thrombosis which is followed by myocardial infarction? How often may this be blamed for the serious clinical picture and how often rupture of a so-called cholesterol abscess? What of the thrombosis itself? Can it be prevented by anticoagulants given over long periods of time? Is there a possible hazard of such therapy if intimal hemorrhages are important? What about recanalization and how much functional value has it in contrast to the development of the collateral circulation? What of the localization and distribution of coronary artery disease as in such a vessel as the anterior descending branch of the left coronary artery? How much do tortuosity and constant kinking of the vessel play a rôle? Must there be fairly generalized atheroma before serious results come? Finally, what about the effect on heart muscle? Is there an importance in the finely scattered coronary insufficiency with fibrosis that may be hard to recognize macroscopically? What is the relationship of ischemia to necrosis and fibrosis? How much ischemia can there be before necrosis occurs?

Finally, we come to the most important subject of all, more fundamental than physiology, pathology, diagnosis, and treatment, namely the etiological factors themselves. We know a little about them, for instance that there is a family incidence of coronary heart disease but how extensive and intensive is that? Is the inheritance one of body build, biochemical difficulties, anatomical structure, physiological variations, or combinations of these, or what? May we eventually be able to select in their youth potential candidates for coronary heart disease, especially in "coronary" families and begin to plan their protection after we are surer of the underlying cause or causes? How important is the somatotype? We have been finding in Boston that it is the mesomorphic young male who is particularly prone to early coronary heart disease while the young ectomorphic male almost completely escapes. How important is the additional factor of endomorphy? What is the relation to weight change? Does increasing weight through the years increase the tendency to coronary atherosclerosis and in this relationship what about

the diet? If the diet plays a rôle with increasing weight is this the result of total calories or of dietary fats per se? How much actually does the ingestion of cholesterol fat have to do with the development of atherosclerosis? It has been shown that a good deal of cholesterol produced is endogenous but is there some protection if the cholesterol intake is kept at a low level? What of other fats than cholesterol?

The question of sex is a very important one and has been moderately well studied statistically. We have found that in coronary heart disease there is a tremendous preponderance among males; under the age of 40 the ratio is 24 to 1, in the forties the ratio is about 3 to 1, and in the fifties it is about 2 to 1; after sixty the ratio is about 1 to 1. What is the cause of this sex difference? Is it inability to metabolize the fats? Is it related to a thicker coronary wall? Is it related to some unrecognized endocrine variation in the sexes?

Of how great importance is the metabolic rate? We have found in the young cases a tendency to a low metabolic rate but just how important is this? What about exercise per se? Can we help to delay the onset of coronary atherosclerosis in individuals subject to it by advising vigorous exercise from early youth on until there is a limitation by symptoms? Is the maintenance of a limited weight more important than exercise or are both necessary? Is there a relationship to race? How much coronary heart disease is there in China, India, Central Africa, etc. in contrast to England, France, and the U. S. A.? If there is a difference is that to be related to race, climate, diet, or activity or to combinations of these things? The great need and importance of a study of geographic pathology are quite evident. Such a field has hardly been tapped. Do climate and weather per se, in combination or separately, have an important influence? Certainly angina pectoris is more common in cold weather but it has not been shown that acute myocardial infarction from coronary thrombosis is so related. What about physical strain and accidents? There are authenticated cases of acute myocardial infarction after some serious accident or strain, but as a rule these accidents occur at rest. What is the exact situation there? How much of a rôle does nervous strain per se play? Tobacco and alcohol have been variously regarded. Tobacco has sometimes been reputed to be a coronary vasoconstrictor but have not the signs and symptoms resulting from so-called tobacco angina been due simply to an increased heart rate which can alter the T-waves of the electrocardiogram and in patients already afflicted with coronary insufficiency induce angina pectoris more readily? Here the question of individuality enters in and we cannot set hard and fast rules as yet. What about alcohol? Heavy users of alcohol have seemed on occasion to be protected. On the other hand, we ourselves have seen, as doubtless you all have, serious coronary heart disease with invalidism and death in heavy and youthful drinkers. Do tea and coffee have any beneficial effect as vasodilating agents? What about occupation? Will 1,000 Vermont farmers have less coronary heart disease than 1,000 New York bankers and, if so,

is it the occupation per se or the diet or the exercise or the tendency for greater obesity among the bankers, which is the important factor?

And lastly, what about the relationship to other diseases? We do know that coronary heart disease and general arteriosclerosis too are more common in diabetics and in gouty patients than in individuals without these diseases. Also hypertension seems to be an aggravating or even perhaps on occasion a precipitating factor, but we need much more intensive study of these relationships. Is there any connection between peripheral arteriosclerosis of the Mönckeberg type and coronary atherosclerosis? We ourselves have found none. Most of my patients with coronary insufficiency have soft radial artery walls and patients with tortuous, beaded radial arteries have been free from coronary insufficiency. Is there an association of any importance between Buerger's disease and coronary atherosclerosis?

One might mention also in passing the problems that still exist about tests for the diagnosis of coronary insufficiency as by exercise and anoxemia in their relation both to symptoms and to electrocardiograms. Another question that might be asked is as follows: Does biliary colic stir up coronary insufficiency in the presence of heart disease, as we think it can, or in the absence of heart disease (by coronary spasm), which we ourselves doubt?

We haven't mentioned prognosis per se or some of the details of treatment for these are now of much less importance than the problems of etiology and pathogenesis. The field is wide open for cultivation. It has been grossly neglected. There are relatively few groups who are currently studying these problems. We need many more investigators and to get them and put them to work we are sure that we can look hopefully to the new interest developed by the increased activity of the Heart Associations of the U. S. A. and other countries, of the U. S. Public Health Service, of foundations supporting research, and of many research laboratories in institutions throughout this country and abroad.

PRESENT STATUS OF AUREOMYCIN THERAPY *

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AUREOMYCIN is the most recent antibiotic to be accepted into the group of antimicrobial agents that are highly effective in the therapy of human infections. The activity of this antibiotic seems to extend over a wider range of infectious agents than that of any of its predecessors. It is effective when given by mouth and has thus far been found to be essentially free of serious untoward effects. The exact field of usefulness of aureomycin, however, still remains to be defined and it will be necessary to accumulate a considerably greater body of well controlled clinical data than are as yet available before the value of this agent in many conditions where it is effective can be compared with that of other antimicrobial agents having similar or overlapping activities. In the time allotted for this presentation, it will be possible only to summarize briefly the present status of aureomycin as based on the reports already published and some more recent experiences.

SOME PROPERTIES OF AUREOMYCIN

While our chief concern is centered on the actual clinical value of aureomycin as demonstrated in the treatment of disease, various properties of this agent must be borne in mind if it is to be used intelligently and to the greatest advantage. The appreciation of some of these characteristics of aureomycin may also be helpful in interpreting certain of the apparently conflicting observations that have been reported.

Aureomycin is produced by a new species of soil organism belonging to the genus *Streptomyces*—the same genus to which belong the organisms that produce two other clinically important antibiotics of wide antimicrobial activity, namely streptomycin and chloromycetin. Duggar,[1] who first described this new species named it *Streptomyces aureofaciens* because of the golden yellow pigment that it produces during a certain stage of its growth, and the antibiotic owes its name to this source and to the fact that it has a similar golden yellow color.

Aureomycin is a weakly basic compound which in the crystalline form is practically insoluble in water but is very soluble in aqueous solution above pH 8.5.[2, 3] It has a molecular weight of 508 and contains carbon, hydrogen, nitrogen, oxygen and nonionic chlorine.[2] Its physical and chemical properties are entirely distinct from

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those of chloromycetin, another new antibiotic which also contains nonionic chlorine and which has many biological activities similar to those of aureomycin.[4, 5]

Stability. Aureomycin is supplied for oral and parenteral use in the form of the crystalline hydrochloride which is soluble in water only to the extent of about 14 milligrams per c.c., making an acid solution of about pH 2.9, but it is much more soluble in alkaline buffer solutions.[2] The antibiotic is highly stable in the dry crystalline form and also when present in high concentrations in acid solutions. It loses its activity rapidly in dilute solutions, in neutral or alkaline solutions and in body fluids that are kept at incubator or room temperature and less rapidly at 5° C. Its activity may be preserved essentially intact even in dilute or slightly alkaline solutions if they are kept in the frozen state at temperatures of − 20° C. or lower.[2, 6-11]

Toxicity in Animals. Aureomycin has a low order of acute and chronic toxicity for the common laboratory test animals [3, 10, 11] although a cumulative toxicity similar to that observed with penicillin has been noted in guinea pigs.[12] Large amounts are well tolerated by animals when given by mouth but some local irritation occurs at the sites of subcutaneous and intramuscular injections and some perivascular irritation may result when it is given intravenously. Large intravenous doses injected rapidly may cause a marked reduction in blood pressure and cardiac arrest. Prolonged administration in animals has produced no significant anatomic or functional changes in the blood, liver, kidneys or nervous system. It produces no changes in the blood pressure or blood sugar levels.

Absorption, Excretion and Distribution. After oral administration in animals aureomycin appears in the urine during the first hour and is actively excreted for six to 12 hours.[3] It has been found in the cerebrospinal fluid of dogs six hours after an intravenous injection,[3] but some observers have failed to detect any activity in the cerebrospinal fluid of laboratory animals after parenteral (presumably intramuscular) administration.[10]

Absorption and excretion studies in adult humans have given results similar to those obtained in animals.[9, 13-16] After single oral doses, the drug appears in the urine in appreciable concentrations during the first hour, in high concentrations between two and eight hours and excretion continues for more than 24 hours. About one-eighth of a single oral dose can be recovered in the urine.[13] Maximum concentrations of 0.6 to 2.5 micrograms per c.c. are attained in the serum between two and four hours after a single oral dose of one gram and concentrations of 5 to 20 micrograms per c.c. of serum are subsequently maintained during continuous oral administration of 1 gram every four or six hours.[16] After intravenous injections the serum level falls rapidly during the first hour and then more slowly,[16] but concentrations of 2 micrograms per c.c. or less are usually demonstrable in the serum after intramuscular doses of 50 to 200 mg.[9, 14, 16] Variable results have been reported with respect to the demonstration of aureomycin activity in cerebrospinal fluid of humans after systemic administration.[16, 17] Appreciable concentrations have been demonstrated in such fluids, however, in a case of meningitis during oral administration of the antibiotic.[17] Aureomycin probably gets into all body fluids [17a] but more information on the distribution of aureomycin in such fluids and in tissues is needed.

In vitro Activity. Aureomycin is highly active in vitro against a wide range of pathogenic bacteria.[1, 6-9, 11, 18] Its activity, like that of other antibiotics varies markedly against different species of organisms and against different strains of the same species. In general, aureomycin is more active against the coccal organisms than against the gram-negative bacilli, but it is highly active against strains of *Hemophilus.* Strains of *Pseudomonas aeruginosa* and most strains of *P. vulgaris* appear to be the most resistant of the clinically significant bacterial pathogens. Against most gram-positive and gram-negative cocci it is definitely less active weight for weight than penicillin, while against most gram-negative bacilli it is less active

than polymyxin and about equally as effective as streptomycin. The activity of aureomycin against any given strain, however, is entirely independent of its sensitivity or resistance to other antibiotics.

The in vitro activity of aureomycin like that of streptomycin increases with the concentration of the antibiotic and diminishes with increasing numbers of exposed bacteria. In contrast to streptomycin, which is more active in an alkaline medium, the activity of aureomycin increases with increasing acidity of the medium. Some substances, like cysteine and semicarbazide, and some constituents of culture media, like glucose and salts which have been shown to interfere with the action of streptomycin do not seem to have any such effect on aureomycin activity.[6] Blood and serum, however, may be antagonistic.[7, 9] Thus far it has not been possible to isolate any enzyme analogous to penicillinase which is capable of inactivating aureomycin. Nor has it been possible to demonstrate the occurrence of highly resistant variants in large bacterial populations of aureomycin-sensitive strains. In the latter respect, and with regard to the production of resistant strains by repeated subcultures in antibiotic-containing media, aureomycin seems to behave more like penicillin than like streptomycin.

Some of the apparent advantages of other antibiotics over aureomycin in the in vitro tests may be due, in considerable measure to the relative instability of the latter under the cultural conditions of the tests. This may account for some of the discrepancies that have been noted when the in vitro sensitivities of bacteria or even the results of certain experimental infections in animals are compared with the clinical results observed in the treatment of clinical infections under conditions where the antibiotic is replenished at frequent and regular intervals. In this regard it is of interest to point out that when organisms are exposed to the products of aureomycin producing strain of *Streptomyces aureofaciens* during the surface growth of the latter, considerably greater inhibiting effects are demonstrated than are otherwise obtainable. In such tests *Mycobacterium tuberculosis*, certain fungi and other organisms are inhibited to a greater extent than they are by a streptomycin producing strain of *Streptomyces griseus* growing under similar conditions.[1]

Antirickettsial and Antiviral Activity. The most striking effect of aureomycin and the one which has been most instrumental in stimulating interest in this antibiotic, however, has been its marked therapeutic activity against infections with all of the known and available rickettsias[19, 20] and the viruses of the psittacosis-lymphogranuloma venereum group[19] in embryonated hens' eggs, mice and guinea pigs. Aureomycin is not effective against these viruses in vitro. In the experimental infections there was an indication of a quantitative relationship between the dosage of the infecting agent and the dosage and time of administration of aureomycin. Early and adequate treatment of infections produced with small doses of these infectious agents apparently resulted in sterilization of the eggs or mouse tissues and the failure to develop antibodies in guinea pigs, whereas animals surviving treatment of infections produced with large doses were found to be immune on reinoculation or to harbor the infectious agents for considerable periods. Aureomycin has been found to be totally ineffective against all of the other viruses that have been tested thus far.[19]

Effect on Experimental Bacterial Infections. The results of treatment of certain experimental bacterial infections in animals with aureomycin have been irregular and for the most part have not compared favorably with the results of similar treatment with polymyxin or streptomycin against some gram-negative bacillary infections and with penicillin against some gram-positive coccal infections.[10–12, 21, 22] Further experiments are needed to determine whether or not this disadvantage was the result of the time-dose relationships used in these studies and whether other dosages might yield different results. In the treatment of experimental relapsing fever in mice and in experimental leptospirosis in hamsters, crystalline aureomycin appeared to be more effective on a weight basis than penicillin.[12]

Clinical Results

The results of the clinical experience that is available to date have indicated that, in general, aureomycin exerts a highly beneficial effect in the treatment of infections with those agents against which the antibiotic has shown activity in vitro or in experimental infections. In some of the bacterial infections, moreover, the favorable clinical results have actually exceeded those which could be expected on the basis of the laboratory tests. There is also evidence, suggestive or convincing in some instances but less definite in others, of considerable benefit in certain infections in which such benefits could not have been predicted on the basis of the laboratory results. It is decidedly premature at this time, however, to make an inventory of all known human infections with respect to the degree of effectiveness to be expected from aureomycin and it would be particularly hazardous to indicate the relative value of this and other antimicrobial agents in the treatment of all these infections. It will suffice here to summarize in a very general way the data thus far available in a few specific infections and in certain groups of infections.

Rickettsial Infections. Published reports are available on the results of aureomycin treatment of 19 proved cases of Rocky Mountain Spotted Fever of the eastern type,[14, 23-25] a similar number of cases of typhus fever either proved or presumed to be of the murine type [26, 27] and of Q fever from northern California [28] and also an isolated case of recrudescent epidemic typhus (Brill's disease).[29] The results in all of the acute cases were essentially similar. Clinical improvement in symptoms of the acute illness usually occurred within the first 24 hours after oral therapy with aureomycin was started. The temperature returned to normal either during or before the third day of treatment and the rash in the cases of typhus or spotted fever usually faded at about this time.

In most of the groups of cases of rickettsial infections that have been reported, the outstanding feature has been the uniformity with which the fever and symptoms subsided in relation to the treatment, irrespective of the time when treatment was begun. Where similar cases that have been treated symptomatically were available for comparison, a marked reduction of the period of acute symptoms, fever and rash and a decided shortening of the convalescent period was noted in the aureomycin treated cases. The results also were decidedly superior to those obtained in similar cases treated with para-aminobenzoic acid. There have been no complications and no deaths in the aureomycin treated cases.

The results in a group of four patients with Q fever that were treated with small intramuscular doses of aureomycin were not considered satisfactory. In Q fever relapses have been observed following premature cessation of therapy, but the patients became and remained afebrile following a second course of aureomycin. In a chronic case of this disease, however, even large doses failed to produce a cure. In murine typhus, there is evi-

dence that an intensive course of oral therapy over a period of 24 to 48 hours yields highly satisfactory results.[27] A comparison of the effects obtained with chloromycetin in rickettsial infections will be discussed by Dr. Woodward.[30]

Lymphogranuloma Venereum-Psittacosis Group. Thus far the most extensive experience with the use of aureomycin in the treatment of lymphogranuloma venereum has been reported from the Harlem Hospital by Wright and his co-workers.[31, 32] Their findings indicate a definite and marked effect in the acute cases and some benefit, particularly as an adjunct to surgical and other measures, in the management of chronic cases. Most of these results were obtained with intramuscular doses given in amounts which would now be considered quite small and probably inadequate. Some of the chronic cases have relapsed after cessation of treatment. Possibly better and more lasting results could be obtained with larger doses given by mouth and maintained over longer periods. In psittacosis, there are as yet no significant data to indicate whether or not the very striking effects observed in the treatment of experimental infections with this virus can be duplicated in the clinic.

Primary Atypical Pneumonia. Aureomycin is the first agent which has been noted to exert a regular and marked beneficial effect on cases of primary atypical (viral) pneumonia. In the 53 cases of primary atypical pneumonia that were reported in the first three published groups of cases uniformly favorable responses were observed in relation to treatment with aureomycin.[33-35] In the great majority of these cases cold agglutinins were demonstrated at the appropriate time in the course of the illness or during convalescence. In most instances the symptoms improved markedly during the first 24 hours and the fever subsided within 12 to 48 hours. In occasional patients in whom treatment was stopped too soon or who received inadequate doses, the fever and symptoms relapsed but then again responded when treatment was resumed.[33, 36] There is some indication that aureomycin therapy may hasten the clearing of the pulmonary lesions.*

Bacterial Pneumonias. Although aureomycin is of particular interest in respiratory infections because of its value in the treatment of non-bacterial pneumonias including psittacosis, Q fever and primary atypical pneumonia, it has also proved highly effective in the various bacterial pneumonias. In pneumonias due to various types of pneumococci, including bacteremic cases, the results of oral therapy with aureomycin have been quite comparable to those obtained with penicillin therapy.[36, 37] Symptoms of the acute illness improve or subside within 12 to 24 hours and the fever reaches normal levels between 12 and 48 hours after this treatment is started. Pneumococci are rapidly eliminated from the blood and sputum.

* In a controlled study reported more recently,[54] a prompt therapeutic response was observed regularly in 22 patients treated with aureomycin, whereas in 20 comparable control cases treated with penicillin there was definite variation in the duration of the disease.

Experience in acute pneumonias due to other bacterial agents is too limited, but favorable results have been obtained in staphylococcal, streptococcal and *Hemophilus influenzae* infections.[36, 38] In some cases with subacute or chronic staphylococcal suppurative infections of the lung, clinical improvement with reduction or elimination of staphylococci from the sputum has occurred after therapy with penicillin, streptomycin and sulfonamides had failed.[36, 38] Aureomycin has been used in more than 35 children with pancreatic fibrosis who had extensive bronchopulmonary infections due to staphylococci. Many of the strains were resistant to penicillin and streptomycin and previous treatment with these agents was unsuccessful or gave only temporary improvement. In these cases, marked improvement with increase in appetite and in weight followed aureomycin therapy and often persisted for as long as two or three months. Infection in these cases usually relapsed and was then associated with pyocyaneus or proteus organisms.[38]

Staphylococcal Infections. In addition to staphylococcal infections of the lung, aureomycin has proved effective in many cases of superficial staphylococcal infections of the newborn [15, 38] and in cases of skin infections complicating acute leukemia [38] or other blood dyscrasias.[36] It has resulted in temporary or prolonged improvement in some cases of osteomyelitis which failed to improve under treatment with penicillin and streptomycin.[36] In many of the chronic cases, relapse has followed the cessation of aureomycin therapy.

Typhoid and Salmonella Infections. Reports are now available on the use of aureomycin in more than 45 cases of typhoid fever and in a few cases of salmonella enteritis and salmonella bacteremias.[14, 15, 25, 39–41] Apparently favorable results have been obtained in about one-half of the cases and stool cultures have become negative for salmonella in almost every instance shortly after treatment was begun and have remained so. The favorable results in this group of cases, however, have not been really dramatic and in many instances there was no obvious benefit. In occasional cases bacteremia has persisted from one to six days after treatment particularly when small doses were used or when there were inaccessible focal infections. Attempts to eliminate typhoid bacilli from a chronic carrier by prolonged oral aureomycin both before and after cholecystectomy have failed.[40] The results thus far available in cases of typhoid fever suggest that chloromycetin may be superior to aureomycin in this disease.[30, 41, 42]

Urinary Tract Infections. Aureomycin is effective in vitro against most of the organisms which are found in urinary tract infections except proteus and pyocyaneus. The results of therapy of cystitis and pyelonephritis have compared favorably with those obtained with other chemotherapeutic and antibiotic agents.[15, 43–45, 55] Aureomycin has eliminated the bacilluria and pyria in many cases that have resisted treatment with sulfonamides and streptomycin. In about one-half of the cases of chronic urinary tract infections, however, particularly those in which there are calculi or other obstructive lesions or where there have been repeated instrumentations and

operative procedures, improvement under aureomycin therapy has been only temporary. In most of these cases proteus and pyocyaneus organisms have replaced the previous aureomycin-sensitive flora and infection in these cases returned and then was benefited only slightly or not at all by further courses of aureomycin.

In an occasional patient the combination of streptomycin and aureomycin has resulted in eliminating bacilluria and pyuria when all previous therapy including these same agents given separately had failed.[36] Aureomycin has the advantage that it is active in an acid medium and in most of the patients that are treated with aureomycin, including those with proteus infections, the urine is moderately or markedly acid.

Brucellosis. Published results are available of the treatment in a small number of acute and active cases of brucellosis with aureomycin.[15, 22, 27] Most of these cases were due to *Brucella melitensis* but one was a recurrent *Brucella suis* infection and in two the type of organism was not specified. All of these patients had rapid clinical remission for periods up to two months, but there have been some relapses in cases of melitensis infections in which small doses were used or the treatment stopped too soon, and a favorable response was again obtained from another course of aureomycin. It is still too soon to judge the permanence of these results. One chronic case did not seem to be benefited by the treatment.[27] In a few cases of *Brucella melitensis* infection there was a temporary febrile reaction associated with a drop in blood pressure. On the basis of some of the early observations, particularly those in which reactions occurred, it was recommended that treatment with this disease be started with small doses and then progressively increasing doses but the dose now recommended is 4 to 6 grams a day for two weeks.[22, 46]

In vitro tests of five strains have shown them all to be sensitive to less than 1 microgram per ml. of aureomycin.[15] Comparative tests in vitro and in embryonated eggs, however, have shown aureomycin to be less active by weight than streptomycin against all types of *Brucella*.[22] In this disease, the clinical results were certainly better than those that were expected on the basis of the laboratory findings and it is now considered that aureomycin is probably the most active agent in this disease and is definitely superior to the combination of streptomycin and sulfadiazine.[22, 46] It is apparently the first agent with which rapid and favorable responses have been obtained regularly in acute cases.[22]

Acute Peritonitis. Aureomycin has been used with considerable success in the treatment of acute generalized peritonitis following appendicitis or perforated ulcers.[47, 48] It has also been used by mouth as a prophylactic agent to prevent the occurrence of peritonitis in patients treated by peritoneal lavage for anuria and nitrogen retention and also in preparation for bowel surgery.[48] As a prophylactic agent it has proved superior to the combination of streptomycin and the poorly absorbed sulfonamides; the total bacterial counts of both gram-positive and gram-negative organisms

in the lower bowel contents drop rapidly and remain persistently low for long periods during oral administration of aureomycin. There is no evidence of the development of a resistant flora and although *B. proteus* and *Pseudomonas* appear in the feces in some patients, they are usually present in small numbers and have not proved troublesome.[36, 43]

Infections of the Eye. Aureomycin in the form of a borate salt has been used alone in 0.5 per cent solution for local instillations for the treatment of superficial conjunctival infections and in conjunction with oral aureomycin hydrochloride in the treatment of corneal ulcers and infections of the deeper structures of the eye. Favorable results have been obtained by Braley and Sanders[49, 50] quite uniformly in cases of conjunctivitis associated with a large variety of bacterial pathogens, in follicular conjunctivitis of unknown etiology and in trachoma. The results in epidemic keratoconjunctivitis were irregular and no beneficial effect was observed in most cases of vernal conjunctivitis. Dendritic (herpes simplex) keratitis responded favorably in most cases as did some cases of uveitis due to lymphogranuloma venereum, others due to unknown causes and two cases associated with scrofuloderms. A limited experience on the Ophthalmic Service of the Boston City Hospital has confirmed the favorable results in cases of ocular infections associated with pyogenic bacteria.[36]

Infections of the Skin. A number of cases of pyodermia of various types, some of them in newborn infants and others in patients with other severe systemic diseases have shown improvement in varying degrees and for varying periods under treatment with aureomycin after failure to obtain benefit from penicillin and streptomycin.[15, 36, 38] Many of the lesions yielded penicillin and streptomycin resistant staphylococci. Cultures from others have yielded mixtures of a variety of organisms or failed to yield significant pathogens. Of particular interest has been the apparent improvement or even complete remission in occasional cases of malignant pemphigus and the rapid clearing of a case of benign familial pemphigus. In some cases of herpes zoster in which treatment was undertaken early, the lesions failed to progress, the pain subsided, new lesions failed to appear and old lesions began to dry up and healed quite promptly after treatment with oral aureomycin was started. It has proved particularly useful in cases with ophthalmic distribution of the lesions. Relapses in herpes zoster have occurred with new lesions reappearing after treatment was discontinued prematurely, but aureomycin has again been given with benefit in some of these cases.[36]

Meningitis. There is some clinical evidence suggesting that aureomycin given by mouth alone or in conjunction with sulfadiazine may be effective in the treatment of some types of bacterial meningitis. Details of such cases are awaited with considerable interest.

Miscellaneous Cases. It is natural that any new microbial agent should be used in the treatment of all types of conditions which resist other available therapy. Some of these conditions may be caused by or associated with infectious agents that are resistant to the drugs previously used but are

sensitive to aureomycin. Under these conditions, temporary or permanent improvement may result from the use of the new antibiotic. Some of these diseases have already been mentioned. Other infections like the bacterial pneumonias have been treated largely from the point of view of investigating the range of usefulness and comparative effects of aureomycin although most of these infections are known to respond favorably to the agents already available. Only brief mention need be made of additional infections in which aureomycin has been used, since in most instances too few cases have been studied to justify even preliminary deductions as to the true value of aureomycin in these diseases.

In acute gonorrhea in males treatment with oral aureomycin is effective but results equal to those usually obtained with a single intramuscular dose of 300,000 units of procaine penicillin have required oral aureomycin doses of 2.5 grams or more given over a period of 36 hours. Failures were frequent when smaller doses or shorter courses were used.[44, 51] Aureomycin was followed by rapid improvement in a case of acute meningococcemia.[37]

Aureomycin has proved effective in treatment of a small number of cases of granuloma inguinale in some of which the lesions had failed to improve on previous therapy.[32]

A definite antispirochetal effect with healing of the lesion was demonstrated in two cases of primary syphilis. In these cases, the organisms were seen in the dark field preparation for longer periods after the treatment was begun than they are usually observed in cases treated with penicillin.[52, 56]

In a group of 10 patients with nonspecific urethritis, good results were obtained by oral aureomycin in only two cases and temporary improvement during treatment occurred in three others.[36, 39]

Aureomycin appears to be more effective than chloromycetin in the treatment of tularemia.[53]

Eleven cases of amebiasis have been successfully treated with aureomycin by mouth and there has been no recurrence of symptoms.[57] No definite benefit was derived from aureomycin in several cases of tuberculous meningitis that relapsed after streptomycin treatment.[26] Temporary improvement during treatment was noted in a cold abscess,[38] and improvement in some cases of scrofuloderma has been noted.[38, 50]

Dosage. Optimum dosage or duration of treatment for most infections has not been determined. In general, an oral dose of 1 gram every four or six hours may be used to initiate treatment in most severe infections in adults and the dose may be reduced to 0.5 gram every six hours after improvement has occurred. The latter dose, however, may be used to initiate therapy in most cases of urinary tract infection. It is by no means certain that such large doses are required in most infections. Reduction in the size of early doses is often necessitated by the occurrence of nausea and vomiting. The administration of chloretone, alkalis or food together with oral doses has sometimes proved helpful in reducing the amount and severity of upper gastrointestinal symptoms. In infants and children the bitter taste of aureo-

mycin may be disguised by administration with sweetened or highly flavored foods such as chocolate flavored milk, sweetened gruels or ice cream.

For intravenous injection, amounts up to 500 mg. may be added to 500 or 1000 c.c. of 5 per cent dextrose in water and injected slowly over a period of one hour or longer. Smaller amounts up to 100 mg. in 10 c.c. of 0.75 per cent sodium carbonate solution may be injected very slowly through a syringe. These may be repeated at 12 hour intervals or more often at first, and oral therapy is given as soon as that becomes feasible. Intramuscular therapy has thus far proved to be quite unsatisfactory. Doses of 50 to 200 mg. may be given in appropriate amounts of alkaline buffered solutions containing leucine and some procaine.

For use in ocular infections aureomycin borate is supplied in the form of a powder which can be made up into 0.5 per cent solution and a few drops instilled into the conjunctival sac at intervals of one or two hours at first and at longer intervals after improvement has occurred. The solution tends to deteriorate and should not be used for more than 24 hours if kept at room temperature or for more than 48 hours if it is kept in a refrigerator. Stable ointments are being prepared for topical applications, but these have not yet received adequate trials.

Resistance. Although aureomycin-resistant strains of organisms such as proteus and pyocyaneus often replace the sensitive flora in the urine, stools, sputa or discharges of patients under treatment with aureomycin, we have not encountered any instance in which initially sensitive strains of pathogenic organisms have increased appreciably in resistance during aureomycin therapy. In all cases in which organisms have been recovered during or after many days or weeks of continuous or intermittent aureomycin therapy, the strains have had essentially the same sensitivity to aureomycin as did the corresponding strains isolated before treatment was started. One instance has been reported, however, in which an increase in resistance from 0.6 to 20 micrograms per c.c. was demonstrated in a strain of *S. typhosa* isolated from the blood of a patient after six days of aureomycin therapy,[14] and a strain of Aerobacter from urine increased four-fold in resistance during several days of treatment.[36]

Toxicity. Serious toxic effects from aureomycin have not been observed. Disturbing gastrointestinal symptoms have occurred, however, in a considerable proportion of cases receiving aureomycin by mouth. Nausea and vomiting in some cases and diarrhea in others have been particularly prominent since the antibiotic has been manufactured on a large scale. The frequency with which these symptoms have been observed has varied markedly in different individuals, with different lots and with the dosage used. Some of these variations suggest that these toxic effects may be the result of some alteration in the drug produced during the process of manufacture and attempts are being made to identify and eliminate the responsible factors. The nausea and vomiting may be reduced by administration together with small doses of chloretone or alkalis or with food. These symp-

toms may occur early in the course of aureomycin administration or only after several doses and they often subside or become less marked as treatment continues. They have rarely interfered with the continuation of therapy though it has often proved helpful to omit doses for several hours and then resume treatment at a lower dosage level.

In some of the early cases there was a tendency to have large, bulky stools and some patients complained of uneasiness or a squirming sensation in the lower abdomen, but diarrhea with several watery stools a day has been observed in some of the cases treated with recent lots. These symptoms have subsided soon after the treatment was discontinued. Pruritus has accompanied the diarrhea in some instances. It is of interest that when diarrhea was present before aureomycin was started in cases of typhoid fever or salmonella enteritis, the diarrhea decreased soon after aureomycin was begun and often subsided as treatment was continued.[40] In children with pancreatic insufficiency, however, there was an increase in the number of stools throughout the period of aureomycin administration although the stools have been less offensive in odor.[38]

There have been no reports of abnormal blood, kidney or hepatic function or of peripheral or central nervous system symptoms attributable to aureomycin therapy. To our knowledge, there have as yet been no instances of fever or rashes that could definitely be attributed to administration of this agent.

Intramuscular therapy has been quite regularly accompanied by pain, induration and tenderness at the sites of injection. The pain and tenderness may be delayed but not entirely prevented by incorporating 0.5 or 1.0 ml. of 1 per cent procaine with each dose. This local irritation has been present to varying extents with all of the diluents that have been used thus far. Perivascular inflammation has been observed in some cases after intravenous injections, but this can usually be avoided by injecting dilute solutions slowly and taking care to avoid extravasation.

Summary and Conclusions

The experience with the use of aureomycin to date has indicated that it is effective in the treatment of a larger variety of infections than any previous agent. Except for gastrointestinal symptoms that may sometimes be bothersome, no serious toxic effects from its use have as yet been noted. The entire field of usefulness of aureomycin and comparisons of its effects with those of other chemotherapeutic and antibiotic agents under various conditions and in the treatment of many specific infections must await the accumulation of further experience.

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CHLOROMYCETIN AND AUREOMYCIN: THERAPEUTIC RESULTS *

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DURING the last 18 months two new antibiotics appeared which have greatly extended specific therapy in the group of infectious diseases. It is of interest that our earliest specific remedies, quinine, mercury, antimony and the salvarsans, were effective chiefly in the larger infectious agents, the protozoa, the spirochetes. With the development of the sulfonamides the bacteria became vulnerable and in particular the gram positive bacteria and especially the coccal groups. The development of the antibiotics with penicillin in the forefront still further extended the field of specific medication without, however, showing much effect upon those diseases caused by the gram negative group of bacilli. With streptomycin certain of the gram negative organisms began to yield and we are still exploring the range of this new drug. It is known, however, that its effect in the still smaller group of infectious agents, the rickettsiae and viruses is slight and of no clinical significance. The two new antibiotics which were referred to, Chloromycetin and Aureomycin, not only have successfully combatted certain important human infections caused by gram negative bacilli but have already shown themselves to be highly specific in all members of the rickettsial group so far tested and furthermore have significant effects on a few of the viral-like agents of disease. In summary, our painfully acquired knowledge of specific remedies began with agents which attack the largest infectious organisms, the plasmodia and *Treponema pallidum* and has extended intermittently with increasing rapidity within the last 15 years so that we now have effective agents for the major bacterial infections, the rickettsial diseases and have even broached the defenses of the viral infections.

Chloromycetin (Pharmacologic aspects and range of activity): Burkholder ‡ first isolated from soil the streptomyces from which Chloromycetin is derived and demonstrated its antibiotic activity. In the research laboratories of Parke, Davis and Company, Ehrlich [1] and his associates further extended studies of the antibiotic activity and prepared the compound in crystalline form to which was given the name Chloromycetin. The compound is neutral containing both nitrogen and non-ionic chlorine. Its solubility in water at 25° Centigrade is about 2.5 mg. per c.c. It withstands

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boiling for five hours and in aqueous solutions over the pH range of 2 to 9 is unaffected by standing at room temperature for more than 24 hours. Chloromycetin is well absorbed from the gastrointestinal tract. Serum levels after oral administration have been found comparable to those obtained by parenteral administration. [2] There are no reports up to the present time of toxic manifestations resulting from the oral administration of chloromycetin. The prolonged intramuscular administration in dogs resulted in a moderately severe anemia without significant changes in the white blood cells and without disturbance in hepatic or renal functions.

The initial studies of the antibiotic spectrum of chloromycetin in vitro and in vivo in animals indicated a wide range of usefulness, particularly in rickettsial and gram negative infections. [3, 4] These investigations demonstrate outstanding effectiveness in rickettsial and psittacosis infection of chick embryos and mice. Among the gram negative organisms showing a considerable degree of sensitivity to this antibiotic are the brucellae, members of the salmonella group and coliform bacteria. It is interesting to point out that up to the present time chloromycetin has not failed to exert great beneficial effect in those clinical diseases whose etiologic organisms have been found sensitive to the agent when tested in the laboratory.

Aureomycin: (Pharmacologic aspects and range of activity): Aureomycin, first isolated by Duggar,[5] is a yellow crystalline antibiotic obtained from the recently characterized mold, *Streptomyces aureofaciens.* It is freely soluble in distilled water at a concentration of 2 per cent and produces a golden yellow solution having a pH of 4.5. The antibiotic is most stable at pH 2 and an unbuffered aureomycin hydrochloride solution at pH 2.9 has been maintained at cold room temperature ± 4° C. for 23 days with no measurable loss of activity. [6] Aureomycin has low toxicity and when administered in intravenous doses of 50 mg. per kg. in dogs, cats, rabbits, guinea pigs and mice no symptoms are observed. Multiple intravenous doses in dogs produce irritation of the perivascular tissues at the site of injection, and subcutaneous and intramuscular injections are likewise irritating. [7] There appears to be no evidence of chronic toxicity when administered for prolonged periods to mice, rats and dogs. [7] After oral administration, aureomycin appears in the urine in one hour and is excreted up to 12 hours. Therapeutically effective concentrations exist in the cerebrospinal fluid within six hours after an intravenous dose. [7] A turbidometric assay has been described for determining the concentration of aureomycin in body fluids.[8] This test has not proved of great value clinically because of the relative instability of this compound.

The in vitro and in vivo range of activity of aureomycin very closely approximates that of chloromycetin. Similarly, its greatest influence is on the rickettsiae and on the viral agents of the psittacosis-lymphogranuloma group.[9] When tested in vitro against brucellae, effective inhibition is demonstrated [10] and most salmonellae are inhibited by aureomycin in the range of 1 to 25 ug. per ml.[11] Both *B. proteus* and *B. pyocyaneus* are relatively

resistant to aureomycin but unlike chloromycetin most strains of gram positive cocci, pneumococci and hemolytic streptococci are actively inhibited by this antibiotic. [12] Aureomycin appears to be bacteriostatic in its effect. Bacteria do not readily become resistant to aureomycin in vitro, nor is there evidence of cross resistance with other antibiotics. [11]

The purpose of this paper is to present personal investigations on the therapeutic effect of these two antibiotics as well as to review the publications of others in this field. The following diseases caused by gram negative organisms have been studied: typhoid fever, undulant fever and tularemia. Studies have been made and published on scrub typhus, murine typhus and Rocky Mountain spotted fever and data are available relative to the effect of these drugs in epidemic typhus and Q fever. Our experience with these agents in the psittacosis-lymphogranuloma group of viral infections is limited but confirms and extends the findings of others. A description of clinical and experimental results follows:

Typhoid Fever

A. Therapeutic results with chloromycetin:

Our initial experience with the beneficial effects of chloromycetin in typhoid fever was published as a preliminary report in August 1948. [13] We are in a position now to report briefly on further typhoid cases which have been treated with this drug. A more complete analysis of all of our data relative to this subject will be reported at a later date.[14]

1. Diagnostic criteria. In all but one of the 21 patients here reported the diagnosis was confirmed by a blood culture positive for *Salmonella typhosa* prior to the initiation of specific therapy. Patients were selected for treatment who were in an active phase of disease and in most instances within the first two weeks of illness. The mean day of illness that treatment was begun in this series of cases was the twelfth day. Stool cultures were performed frequently. The course of disease after the start of chloromycetin administration was followed by observations on the clinical condition, the duration of fever and the results of repeated blood, stool and urine cultures.

2. Method of administration and dosage: Chloromycetin was administered orally in the form of 0.25 gm. tablets and capsules furnished by the Research Division of Parke, Davis and Company. The bitter taste of the original tablets has now been obviated by the use of gelatin capsules. The initial dose was large, gauged on the basis of approximately 50 mg. per kilo body weight. After the intial dosage the drug was given in 0.25 gm. doses at variable intervals but usually every two to three hours. Certain of the early cases were first given the antibiotic on a two hour schedule which was changed to the longer interval when improvement was noted. The program of treatment adopted included continuation of the drug for five days after the temperature had reached normal levels. In certain instances we were forced to discontinue treatment earlier because of exhausted supplies. Vomiting of the drug on initial administration occurred rarely but in no

instance necessitated discontinuance of therapy. The average total dosage per patient was 22.7 grams given over a period of 9.1 days.

3. Results:

a. Clinical: Insofar as the patients' response to therapy is concerned there was little subjective improvement within the first 48 hours of treatment. By the third day, however, there was obvious abatement of headache, cough and delirium and it was apparent on the fourth day that the patient was in convalescence showing interest in his surroundings, with increased strength and appetite. Rose spots noted in approximately half of the patients were observed to disappear by the end of the second treatment day.

The recorded data relative to the effect on the febrile course constitute striking evidence of the therapeutic effectiveness of chloromycetin in typhoid fever. Irrespective of the height of the preceding fever, the age of the patient, or the day of illness treatment was begun, chloromycetin therapy was followed in all instances by fall of temperature to normal levels within 4.5 days after the inital dose (table 1). The average duration of fever after initiation of therapy was considerably less, approximately 3.5 days. Normal temperature was defined as oral temperature remaining under 99° F. and rectal temperature under 100° F. In all instances reduced toxicity paralleled or preceded the return of temperature to normal.

b. Laboratory: In 20 patients blood cultures taken prior to initiation of specific therapy were positive for *S. typhosa*. In 18 of the 21 cases blood cultures were taken daily for three to five days following the initiation of treatment. In four patients blood cultures were found positive, two during the first 24 hour period and two during the second 24 hour period. The subsequent cultures remained sterile except in the case of patients who suffered a relapse.

Stool cultures were obtained at frequent intervals, and no patient was discharged without three consecutive negative stool cultures having been recorded. Positive cultures were obtained in six patients at least one time while chloromycetin was being administered and in four patients after the antibiotic had been stopped. The stools of all four relapse patients contained *S. typhosa*. Urine cultures before the beginning of specific therapy, during therapy and in convalescence were consistently negative.

The blood level for chloromycetin was followed in 17 patients throughout the course of treatment. The blood concentration of the drug during the first 24 hours of therapy, already reported in 10 cases, [13] was of the order of 30 to 80 gamma/ml. and during the subsequent three to five days averaged 20 gamma/ml. The concentrations in the remaining seven cases are comparable. Workers at the Research Division of Parke, Davis and Company had previously shown that *S. typhosa* is inhibited by concentrations of chloromycetin of approximately one-quarter gamma/ml. when the 50 per cent end point technic is applied to fluid culture. [4] Utilizing practically identical methods, we found the sensitivity of the infecting organisms in this series to range from .25 to .26 gamma/ml. In no instance when additional

tests were made on organisms causing a relapse or after termination of chloromycetin therapy was in vitro resistance of the organism observed.

4. Occurrence of complications:

a. Evidences of incomplete sterilization: The evidence shown above indicated that the clinical manifestations of typhoid fever were definitely suppressed by use of the drug and moreover in the majority of cases the evidence indicates complete disappearance of the typhoid bacillus from the blood stream and from the stool. This abolition of the typhoid bacillus was evident in 13 of the 21 cases.

However, that such complete sterilization was not always attained is evidenced by the data concerning the remaining eight cases. In four instances follow-up stool cultures were found positive on at least one or two occasions. In four cases positive blood cultures recurred and in all of these the reinvasion of the blood stream was evidenced by clinical relapses. There were four relapses in 21 cases, the recurrences beginning on the ninth, twelfth, thirteenth and thirteenth days, respectively, following discontinuance of treatment. It is of considerable importance that in three instances the organisms found during the relapse were tested and found not to have lost their sensitivity to chloromycetin. This was confirmed in three cases by the treatment of the relapse with chloromycetin with resultant prompt clinical cure.

b. Complications: It should be noted also that certain of the usual complications of typhoid fever may occur either during treatment or after treatment has been discontinued. In two instances intestinal hemorrhage was observed after the patient had become afebrile but was still under treatment. In another case perforation occurred under the same circumstances. It is of interest to note that in this patient with all the clinical characteristics of perforation, the peritonitis was overcome without surgical treatment, apparently as a result of continued chloromycetin treatment supplemented by penicillin and streptomycin. Another instance of what may have been a late typhoid complication was that of an elderly man who after discharge from the hospital as cured of typhoid returned in 10 days with low grade fever and died suddenly with a massive pulmonary embolus (confirmed by autopsy) which was suspected though not proved to have originated from a late typhoid phlebitis.

c. In summary then the evidence to date indicates that the presently used schedule of chloromycetin therapy in typhoid fever is highly specific in so far as its uniformly favorable and striking influence on the acute clinical infection. However, under this regime it is also evident that a certain percentage of cases are not completely freed of the typhoid bacillus so that relapses may occur and positive stool cultures without relapse may be observed. Moreover, the lesions produced by the initial infection of the intestinal tract have not so promptly healed as a result of the specific therapy as to insure against such mechanical ruptures of tissue as may cause complicating perforation or intestinal hemorrhage.

5. Illustrative case reports:

Case 1 (*figure 1*). *Response in a typical patient:* A 24 year old Chinese girl first treated on the ninth day of illness. The early course was characterized by fever, headache, an irritative non-productive cough, and toxicity. Significant physical findings when examined in hospital were a toxic, dehydrated patient, râles in both lung bases, a slightly distended abdomen and a soft palpable spleen. The pretreatment blood culture was positive for *S. typhosa*, albuminuria was present, the white blood count was 2,850, red blood count 4,060,000. On the ninth febrile day an initial dose of 3.0 grams of chloromycetin was given orally with subsequent doses of 0.25 gram every two hours. Treatment was continued for five days after the temperature became permanently normal. The total amount of antibiotic used was 21.5 grams given over nine days. The course of disease and essential laboratory findings are detailed in figure 1. Lowered toxicity was apparent within 36 hours and within 60 hours the temperature reached permanent normal and the patient was clearly convalescent. Post treatment blood cultures taken at 6, 18, 42, 66, 90, 114 and 138 hours were sterile. On the fifth and twelfth days after initiation of specific therapy the stools were found positive for *S. typhosa* but thereafter were negative. Convalescence was rapid and relapse was not observed.

Case 15 (*figure 2*). *Typhoid fever with relapse:* A 28 year old colored female first observed on the seventh day of an illness characterized by high continuous fever, headache, slight cough, slight abdominal pain and loose, mushy bowel movements. At the time of hospitalization the patient was extremely toxic and disoriented. Râles were heard in both lung bases. Two pretreatment blood cultures grew *S. typhosa* and one stool examined was likewise positive. An initial dose of 2.0 grams of chloromycetin was given on the ninth day of illness. Subsequent doses of 0.25 gram every three hours were administered (supplies of chloromycetin were practically exhausted but it

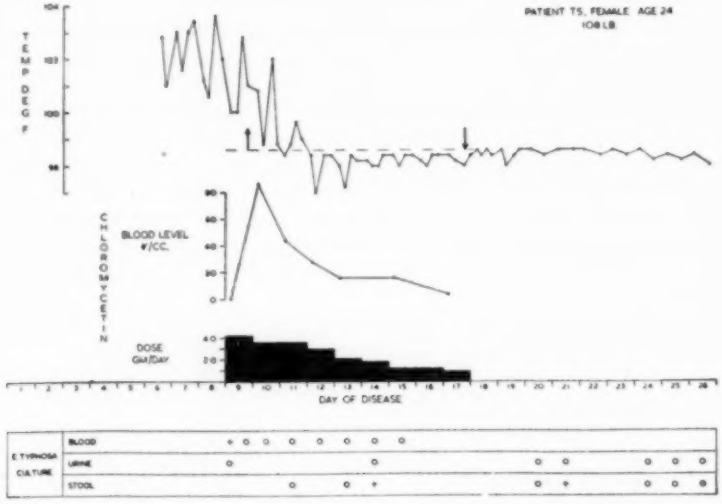


FIG. 1. *Case 1.* Typhoid fever. Chloromycetin. Typical course of typhoid in a patient first treated on the ninth day of illness. In spite of a positive stool during convalescence there was no relapse (Reprinted from Ann. Int. Med., 1948, xxix, 133).

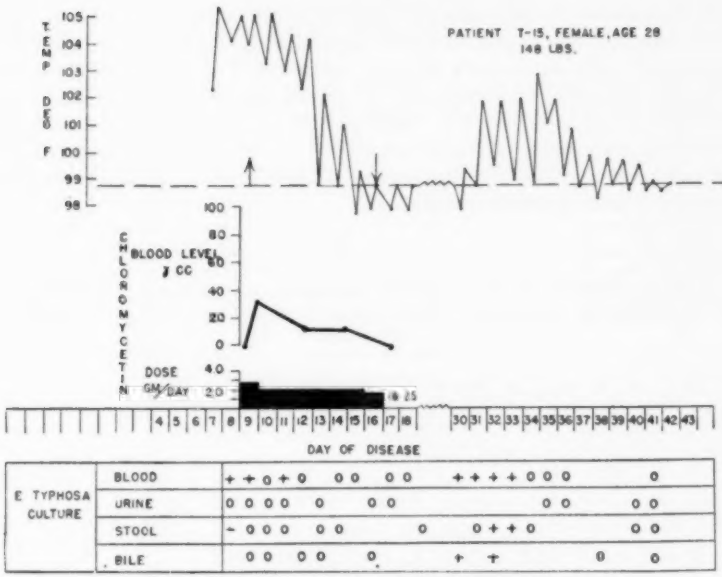


FIG. 2. *Case 15.* Typhoid fever. Chloromycetin. Course of typhoid in patient inadequately treated with chloromycetin. Relapse occurred on thirty-second day of illness. Culture of bile and blood positive for *S. typhosa* prior to relapse. (Courtesy U. S. Army Scrub Typhus Team.)

was felt advisable to spend all that remained on this seriously ill patient). The antibiotic was discontinued on the sixteenth day of illness after 16.25 grams had been employed. It will be observed in figure 2 that the temperature reached normal after 4.5 days of treatment and that the drug was given for only 2.5 days thereafter. Nevertheless the bedside appearance of the patient was improved on the second post-treatment day as evidenced principally by lowered toxicity and better appetite. The temperature remained normal until the thirty-first day from onset of illness when a slight elevation was observed and on the following day a high fever denoted a true relapse. The bacteriological findings are instructive. *S. typhosa* was cultured from the bile (obtained by duodenal tube) and the blood two full days prior to the febrile relapse. Shortly thereafter the stool was again found to contain typhoid bacilli. The febrile relapse lasted 10 days and ended uneventfully. The case well illustrates a relapse resulting from an inadequate course of chloromycetin, the primary response having been favorable.

b. Therapeutic results with aureomycin:

1. Diagnostic criteria: The criteria utilized for the chloromycetin series were adhered to in this smaller group of four patients who constitute our personal experience with the therapeutic effect of aureomycin in typhoid fever.

2. Method of administration and dosage: The aureomycin supplied by the Lederle Laboratories Division of the American Cyanamid Company was in gelatin capsules of 0.25 gram. The capsule was swallowed with ease and

in no instance was it necessary to incorporate the yellow powder in an additional vehicle. The nausea and gastrointestinal irritation reported by others were noted. We employed a large initial dose of 1 to 2 grams followed by a schedule providing from 0.50 to 0.70 gram every four hours in adults and 0.25 gram every four hours in children. The time interval of four hours during the acute phase of illness was rigidly adhered to. In non-fatal cases treatment was continued for two weeks. Details of duration of therapy, total dosage, etc. are represented in table 1.

TABLE 1

Tabulation of Results on the Use of Chloromycetin and Aureomycin in Typhoid Fever

Case	Age	Sex	Day of Illness Treatment Begun	Duration Fever after Beginning Treatment	Last Febrile Day of Illness	Antibiotic		Blood Culture	Relapses	Deaths
						Total Days	Total Grams			
Aureomycin										
1	34	M	12	38	50	14	59.0	Pos	0	0
2	7	M	15	7	22	7	13.8	Pos		Death
3	6	F	15	11	26	13	22.2	Pos	0	0
4	42	M	16	3	19	3	13.0	Pos		Death
Mean	22		14.5	24.0 (2 cases)	38.0	9.0	27.8		0	50%
Chloromycetin										
Mean for 21 cases	23.2		12.0	3.5	16.2	9.1	22.7		4	0

3. Results:

a. Clinical: Improvement in symptoms was not apparent in these four patients. An antipyretic effect resulting from aureomycin was observed in two patients but it is to be emphasized that during this period of lowered temperature, the toxic typhoid state continued and no improvement was apparent. In the two non-fatal patients the pyrexia recurred after a brief respite in spite of the same continued dosage of aureomycin. The entire febrile course in these two patients was 50 and 26 days respectively. Two patients in this group died. One, a seven year old boy, succumbed to the toxemia of the disease on the twenty-second day of illness after having received a total of 13.8 grams of aureomycin in seven days. (His sister treated with chloromycetin made a rapid recovery.) The second fatal case was a 42 year old male who died on the nineteenth day of illness after having received 13.0 grams of aureomycin for three days prior to death.

b. Laboratory: In all instances the diagnosis of typhoid fever was confirmed by isolation of *S. typhosa* prior to the beginning of specific treatment. In case 25, presented in limited detail below, the organism was isolated from

the blood one, two, five, and six days after starting aureomycin. The stools after the first treatment day remained free of typhoid organisms.

4. Occurrence of complications:

Two of the four patients treated with aureomycin died on the nineteenth and twenty-second days of illness. Complications in the two surviving patients were not observed.

5. Illustrative case report:

Case 25 (figure 3): A 34 year old white man hospitalized on the fifth day of illness. The first 12 days of disease were characterized by headache, high continued fever, cough without expectoration, and delirium beginning during the second week of illness. On the twelfth day when aureomycin was started there was a distinct malar flush, the patient was extremely toxic, râles were present in both lung bases and abdominal distention was slight. An initial oral dose of 1.0 gram of aureomycin was

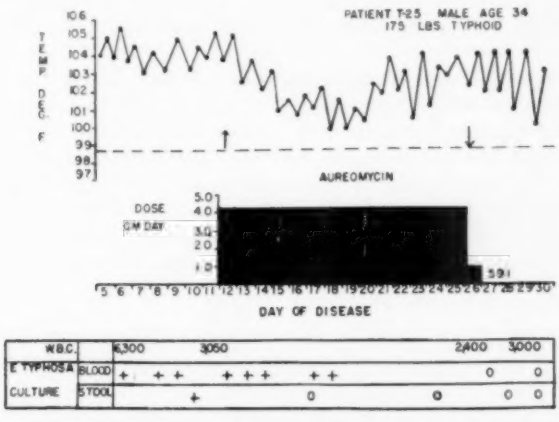


FIG. 3. *Case 25.* Typhoid fever. Aureomycin. Course of disease in patient treated with aureomycin. The antibiotic produced temporary moderate antipyretic effect without improvement of general condition. Bacteremia continued for first seven days of treatment. Temperature became normal on fiftieth day after onset.

given followed by 0.7 gram every four hours for 13 days. A total of 59.1 grams was given. Nausea was experienced but all of the medication was retained. An antipyretic effect of the drug is observed in figure 3 with the temperature reaching a lower level of 100° F. In spite of this apparent improvement, the delirious toxic state continued and the blood persisted in showing *S. typhosa*. Without a change in dosage the high level of pyrexia returned and the course of typhoid continued unaltered. The entire febrile course in this patient was 50 days, or 38 days of fever after beginning the administration of aureomycin.

C. Discussion:

Except for our preliminary publication [13] there are no other reports on the effect of chloromycetin in typhoid fever.

Ross et al. [15] report in detail the findings in three patients with typhoid

treated with aureomycin. They conclude that aureomycin did not produce any perceptible reduction in the duration of illness in two patients but suggest that the acute phase in a third case may have been favorably influenced. Finland et al. [16] detailing the results of aureomycin in five patients with typhoid conclude that the therapeutic effects were equivocal. Both of these groups of workers report the clearing of the blood and stool of typhoid bacilli after several days of aureomycin treatment.

Although the two series of patients reported in this present study are not comparable from point of view of number, it appears that the response to treatment is in sharp contrast. With chloromycetin therapy there is a uniform pattern of response with the temperature returning to normal on an average of 3.5 days when adequate doses of drug are employed. An improved clinical state precedes the defervescence. Aureomycin in our hands has not altered effectively the course of disease and two patients died after having received this antibiotic for three and seven days respectively, prior to death.

An inadequate course of chloromycetin results in clinical relapses and in 21 cases here reported four relapses occurred in patients receiving the antibiotic for 7.5 days or less. In three patients with relapses retreated with chloromycetin a prompt, favorable response was again observed. Chloromycetin is clearly the drug of choice in clinical typhoid. The optimum course of treatment remains to be determined.

Brucellosis

A. Therapeutic results with chloromycetin:

1. Diagnostic criteria and number of cases: Eight patients manifesting evidence of active infection with brucellosis have been treated with chloromycetin. Treatment was initiated when the clinical evidence available suggested brucellosis and when laboratory findings were confirmatory. Confirmation of the clinical diagnosis was sought in each instance through the following procedures: (1) Blood was taken from the patient for culture before the administration of specific therapy. The special cultural methods routinely employed in brucellosis were used. Blood cultures were repeated on each patient at least three times during the period of hospitalization and one month following discharge from the hospital. (2) Agglutination tests utilizing *B. abortus* as antigen were performed by the usual laboratory technics.

2. Method of administration and dosage: The dosage regime adopted for the study was empirical and based, in general, upon prior experience in scrub typhus [17] and typhoid fever [13] as outlined above. The initial dose based on approximately 50 mg./kilo body weight was adhered to and the subsequent schedule was 0.25 gram given every three hours until at least five days of normal temperature ensued. In all instances the antibiotic was tolerated well orally and no clinical evidences of toxic effects were observed. The

average total dosage per patient was 19.7 grams given over a period of 8.1 days.

3. Results:

a. Clinical: The mean duration of fever prior to treatment in the eight treated patients was 30.7 days. Two of these patients were more seriously ill than the others. Within 36 hours after the start of specific treatment they were resting more comfortably, spent a more restful night for the first time since the onset of illness, and diaphoresis was greatly reduced. In the remaining six patients there seemed to be immediate improvement of the body and joint pain, added strength, and a decidedly improved taste for food. In the eight patients the mean duration of fever after beginning chloromycetin treatment was 2.4 days. The spleen, found enlarged in six patients, was observed to become nonpalpable during the course of antibiotic treatment or shortly thereafter. See table 2 for tabulation of statistical results.

b. Laboratory: (1) Of the eight cases constituting this series of treated patients, four showed a positive blood culture for *B. abortus* and two for *B. suis* prior to initiating treatment with chloromycetin. All of the post-treatment blood cultures remained sterile. In all patients a significantly high rising titer for brucella agglutinins was demonstrated (table 2).

(2) Results of sensitivity tests. The sensitivity of the infecting organisms isolated from the five patients ranged from 0.78 to 2.4 gamma/ml. These concentrations compare favorably with those reported by Smith et al. [4] who have previously demonstrated inhibition of brucellae by chloromycetin in the following concentrations: *B. abortus* 2.0 gamma/ml., *B. suis* and *B. melitensis* 0.5 gamma/ml.

4. Occurrence of complications:

This small group of patients has shown no complication attributable to brucellosis. A period of eight months has now lapsed since six of these patients were treated. A relapse of symptoms has not been observed, the patients are ambulatory and afebrile, and blood cultures taken on the three month follow-up examination remain sterile. It is of interest that during this same period the agglutination titers have uniformly decreased.

5. Illustrative case reports:

Case 1 (*figure 4*): A 27 year old colored man gave a history of drinking raw milk. The patient was hospitalized at Fort Meade on the thirty-ninth day of illness. His early complaints were primarily those of fever, profuse sweating, headache, anorexia, general weakness and malaise. After admission the evening temperature reached 105° F. and ranged from 102° to 105° prior to the administration of specific therapy. His nights were restless because of pyrexia, sweating and general aching. There were no signs of a localized infection. On the fifty-second day of illness the blood culture was found positive for *B. abortus*. The organism was sensitive to chloromycetin in the concentration of 2.4 gamma per c.c. At this time the serum agglutination for *B. abortus* was 1/2560. The spleen was quite readily palpable and there were scattered râles throughout both lungs. Chloromycetin was given orally with an initial dose of 3.0 grams and a subsequent dosage of 0.25 gm. every three hours. The drug was well tolerated. On the first night of drug treatment the patient was more

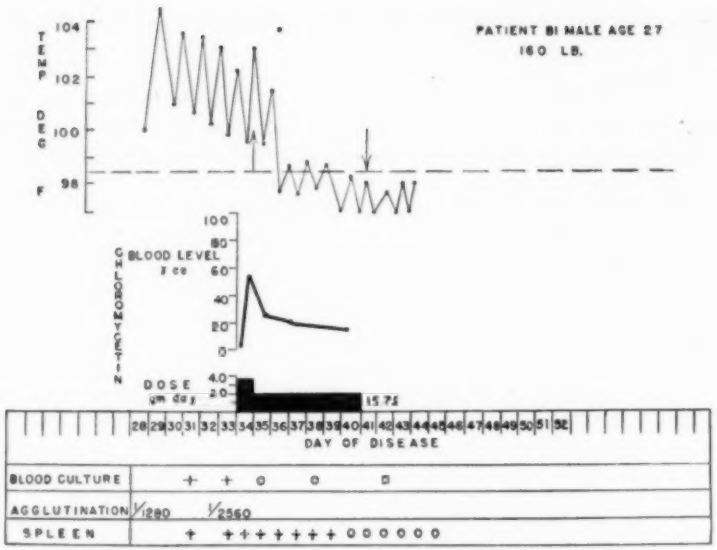


FIG. 4. *Case 1.* Brucellosis. Chloromycetin. Response to treatment in patient with brucellosis of abortus type. Causative organism found sensitive to chloromycetin in concentration of 2.4 gamma/ml.

comfortable and diaphoresis was greatly reduced. On the following day the appetite was decidedly improved, and the bedside appearance was brighter. The evening temperature reached normal 48 hours after institution of treatment and remained normal thereafter. The spleen could not be felt after five days of therapy. A total of 13.25 grams of chloromycetin was administered, the course extending to the end of five days of normal temperature. Three blood cultures taken during the convalescent period were sterile. The patient was discharged 25 days after the institution of chloromycetin treatment and remains free of symptoms.

Case 5 (figure 5): A 29 year old white man developed undulant fever after drinking raw milk. The acute illness was characterized by upper abdominal pain, nocturnal fever, anorexia and general malaise. Blood taken on the twenty-second and twenty-third days of illness revealed *B. abortus.* The organism was found sensitive to chloromycetin in the dilution of 0.78 gamma per c.c. The serum agglutinating titer was 1/320. Before institution of treatment the evening temperature ranged from 102° to 104.5° F., the patient appeared quite toxic and had little inclination to eat. Sweating was moderately severe. Three grams of chloromycetin were given orally on the twenty-third febrile day. The subsequent oral dose was 0.25 gram every three hours. The temperature reached normal after three days of antibiotic treatment and the general appearance was improved in half this time. The appetite rapidly returned and diaphoresis was lessened. On the fifth afebrile day the serum agglutinating titer for *B. abortus* was 1/640. Blood cultures taken on the second, third, seventh, eighth and fortieth post treatment days were sterile. Six weeks after discharge from the hospital, examination revealed a healthy patient who had no complaints. At this time the spleen was not palpable, and the blood was sterile. Of added interest a brucellergin skin test performed during the afebrile period was negative.

B. Therapeutic results with aureomycin:

1. Diagnostic criteria and number of patients: Five patients with acute undulant fever treated with aureomycin are included in this series. Except in one instance when repeated laboratory tests could not be performed, the criteria outlined for the above group were adhered to.

2. Method of administration and dosage: The schedule of treatment outlined for typhoid fever was slightly altered. An initial oral dose of one gram of aureomycin was given followed by a dose of 0.5 gram every four hours for three days and then 0.5 gram every six hours for an additional five to 11 days. In one instance because of exhausted supplies, a short course of eight days was given. The average total dose per patient was 21.99 grams given over a period of 11.6 days (see table 2). No clinical evidences of toxicity were observed other than nausea and occasional vomiting and diarrhea already referred to.

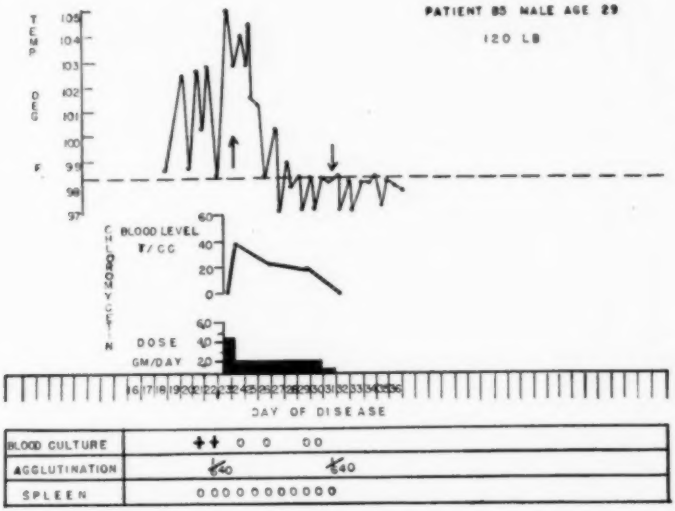


FIG. 5. *Case 5.* Brucellosis. Chloromycetin. Course of illness in patient severely ill with brucellosis, abortus type. Temperature returned to normal 72 hours after beginning chloromycetin. No recurrence after six months' observation.

3. Results:

a. Clinical: The mean duration of fever prior to treatment in the five patients was 39 days. The response to treatment in these patients closely parallels the pattern observed with chloromycetin. Within 48 hours after instituting treatment clinical improvement was noted, the patients uniformly felt stronger, and there was a noticeable increase in appetite and vigor. Aching of the muscles and joints lessened, and the nocturnal diaphoresis was

considerably lessened within 48 hours of beginning treatment. In all five of these patients the PM temperature for at least one week prior to the institution of treatment was 102° F. or above. The mean in the five patients for duration of fever after beginning aureomycin was 3.8 days. The fever in no instance recurred once a permanent normal level was attained. In two patients the spleen was observed to become non-palpable during the course of treatment.

TABLE II

Tabulation of Results on the Use of Chloromycetin and Aureomycin in Brucellosis

Case	Age	Day Illness Therapy Begun	Duration Fever after Therapy	Last Febrile Day of Illness	Size of Spleen	Antibiotic		Agglutination		Blood Culture	Sensitivity γ/c.c.	Maximum Bl. Level γ/c.c.
						Total Days	Total Grams	Acute	Conv.			
Aureomycin												
1	35	17	3.5	21	0	12.0	20.1	320	1280	abortus	.45	
2	32	42	3.0	45	++	8.0	11.35	1280	1280	0		
3	40	93	5.0	98	+	14.0	28.5	640	1280	abortus	.24	
4	40	27	5.5	32	0	12.0	26.0	320	1280	0		
5	37	15	2.0	17	0	12.0	24.0	640	1280	0		
Mean		39.0	3.8	42.6		11.6	21.99					
Chloromycetin												
1	27	53	2.0	55	++	6.0	13.75	1280	2560	abortus	2.4	50
2	31	12	2.0	14	+	6.0	11.25	80	1280	0	0	18
3	21	25	2.5	27	+++	9.0	19.25	640	2560	suis	0	12
4	28	19	2.0	21	++	6.0	15.50	320	1280	suis	1.2	10
5	29	23	3.0	26	0	8.0	19.0	640	640	abortus	.78	33.5
6	38	57	4.0	61	+	12.0	24.75	1280	1280	abortus	1.2	24.8
7	24	32	2.0	34	+	10.0	29.0	1280	1280	abortus		16.0
8	31	25	2.0	27	0	8.0	25.0	640	640	0	0	—
Mean		30.7	2.4	33.1		8.1	19.7					

b. Laboratory: Blood cultures in two of the five patients were found positive for *B. abortus* prior to treatment. Cultures taken several times during the course of treatment were sterile, and in three patients cultures taken one month following discharge were negative. In four patients a rising titer for *B. abortus* agglutinins was demonstrated and in the fifth a titer of 1/1280 was found after repeated tests. The sensitivity of the two organisms isolated from two patients were 0.45 and 0.23 gamma/ml. respectively.

c. Occurrence of complications: Complications were not encountered. Two patients are now four and five months convalescent, and three patients are now about two months past treatment and all remain well.

5. Illustrative case reports:

Case 7 (figure 6): A 35 year old white woman became infected while engaged in the handling of beef at a packing company. The early illness was characterized by

weakness, evening temperature with sweats, moderately severe upper abdominal pain, headache and stiffness of the neck and back muscles. The past history was negative for related disease. The patient was hospitalized on the ninth day of illness. Laboratory studies: white blood cells 4,950; urinalysis negative; chest roentgenogram negative; agglutination with *B. abortus* 1/320 on the tenth day of illness and 1/1280 on the fourteenth day. Blood taken for culture on the sixteenth day contained an organism identified as *B. abortus* which was found sensitive to aureomycin in the concentration of 0.45 gamma/ml. Specific therapy was started on the seventeenth day of illness with an initial oral dose of one gram and 0.5 gram every four hours for two days. The antibiotic was then given 0.5 gram every six hours until the twenty-eighth day of illness. The total dose given was 20.1 grams over a 12 day period. The course of disease is represented in figure 6. Except for a single elevation to 99.6° F., the temperature was permanently normal 3.5 days after beginning treatment. Symptomatically the muscle aches and headache were lessened within 48 hours and sweating reduced. Strength was rapidly regained, the appetite was quick to return and convalescence proceeded uneventfully. Several blood cultures during this period were sterile. A follow-up examination at one, two and six months revealed no evidence of recurrence.

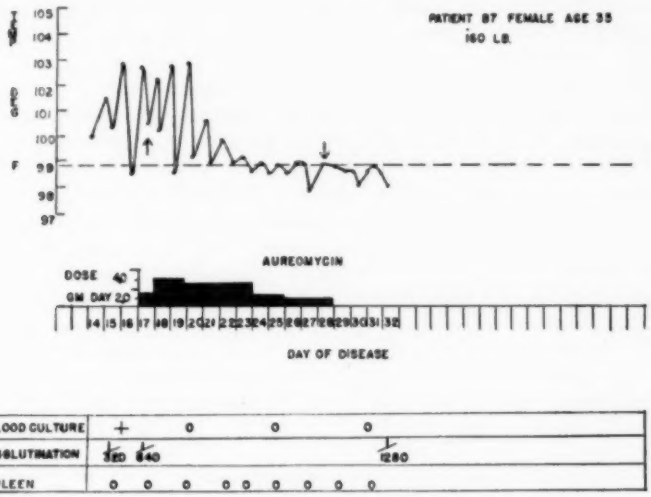


FIG. 6. *Case 7.* Brucellosis. Aureomycin. Response to aureomycin in a 35 year old woman with brucellosis of abortus type. Diagnosis confirmed by positive blood culture and rising titer of agglutinins.

C. Discussion:

Spink and his associates [18, 19] utilized the fertilized egg to demonstrate that a combination of streptomycin and sulfadiazine eradicated *Brucellae* from the tissues of infected embryos, whereas either drug used alone was incapable of achieving this effect. The clinical use of these combined agents in patients with brucellosis yielded more satisfactory results than had any prior treatment. Spink et al. [19] state that in the febrile patient normal tempera-

tures were not sustained until after seven to 10 days of therapy. Relapses with this form of treatment have been observed by others and in our series of 13 patients treated with chloromycetin and aureomycin two had received treatment at an earlier date with the streptomycin and sulfadiazine regime and were in active relapse, with positive blood cultures, when placed under treatment with the new antibiotics. Bryer et al. [19] reported *B. abortus* and *B. suis* sensitive to aureomycin in the concentration of 0.75 gamma/ml. They reported a favorable response to this antibiotic in a patient with chronic *B. suis* infection. The patient became afebrile in three days, and blood cultures became sterile 48 hours after treatment was begun. Ross et al. [15] similarly describe a favorable response to aureomycin in a 48 year old farmer with an acute exacerbation of chronic brucellosis and a positive blood culture. The temperature reached normal in three days and he appeared symptomatically normal within five days. Later blood cultures were sterile. Spink et al. [20] give detailed accounts of a larger series of patients treated in Mexico. In 24 patients with *B. melitensis* infection aureomycin produced prompt reduction of toxemia and return of temperature to normal in 72 hours. Three relapses were later observed.

Our experience with the use of aureomycin in five cases with brucellosis coincides closely with the above reported findings. We have observed a prompt improvement of all symptoms and a return of temperature to normal in 3.8 days. Slightly better results have been obtained in our hands with chloromycetin from the point of view of temperature response, with a mean duration of fever of 2.4 days after beginning treatment. Symptomatically, both antibiotics seem to exert similar favorable effect in amelioration of the symptoms of this disease, and it is not possible to affirm from the small series treated which drug is more effective. Long term follow-up of a large series of patients, varied treatment schedules and observations for possible toxic effects will need study before the effect of these agents can be properly evaluated, in a disease so variable in its clinical manifestations. There has been no opportunity to treat the more virulent melitensis type of brucellosis with chloromycetin.

Tularemia

A. Therapeutic results: We have published elsewhere our results with aureomycin in tularemic infections. [21] These data which include the comparative results with chloromycetin and streptomycin in experimental mouse infection may be summarized by stating that aureomycin has apparently a more effective protective action against *B. tularense* in mice than streptomycin. Under the same conditions the protective action of chloromycetin appears to be less than that of streptomycin or aureomycin.

We have employed aureomycin in three cases of human tularemia, but have not yet had an opportunity to treat a case with chloromycetin.

1. Diagnostic criteria, methods of study and dosage:

Three patients with tularemia were treated. Confirmation of the clinical diagnosis was attempted in each case, when feasible, by inoculation of sputum, blood and material aspirated from an ulcer or bubo into experimental animals and by culture on blood glucose cystine agar. Agglutination tests were also performed. The course of illness after the start of specific therapy was followed by observations on the clinical condition, by blood counts and by urinalysis.

The schedule of treatment with aureomycin conformed closely to that employed in undulant fever. An initial dose of one gram was given with subsequent doses of 0.5 gram every four hours. In the patient described in limited detail below a different schedule was employed because of the severity of the disease.

2. Results (clinical, laboratory and complications):

The three patients, each seriously ill with tularemia, responded satisfactorily to a course of aureomycin. The ulcero-glandular form of the disease complicated by a bilateral pneumonia was present in one case (case 1), and two patients were of typhoidal type, both with pneumonia. The response to treatment in all was immediately favorable; within 24 hours the degree of toxemia was greatly reduced and the signs of weakness, cough and anorexia rapidly improved. The average duration of illness prior to treatment was 9.6 days, and the average duration of fever after beginning aureomycin was 2.5 days.

Laboratory confirmation of a specific diagnosis for tularemia was obtained in each case. *B. tularense* were obtained from the sputum of two patients through mouse inoculation, and from the other patient when pus from the primary ulcer and bubo was inoculated subcutaneously into the same animals. Agglutinins in high titer ranging from 1/1280 to 1/5120 were demonstrated in all patients.

The development of pleural effusion was the lone complication in one instance. The fluid after animal inoculation failed to produce infection. The further course in the patient was uneventful.

3. Illustrative case report:

Case 1 (figure 7): A 53 year old colored man contracted the disease from skinning a rabbit. Malaise, fever and cough were noted in five days. He was hospitalized on the twelfth day of illness in a toxic semi-delirious state. The temperature was 103.5° F., respirations were rapid, dehydration was extreme, speech was muttering and there was moderate stiffness of the neck. Breath sounds were suppressed and numerous râles were heard bilaterally. A roentgenogram revealed bilateral pulmonary infiltration of the patchy, lobular type. A small fluctuant area was present on the right index finger, and large tender glands were present in the right axillary and epitrochlear regions. Material from these areas was taken for animal inoculation. Aureomycin was started on the evening of admission with an initial dose of 100 mg. intramuscularly and 0.75 gram by stomach tube. The dosage regime may be followed in figure 7. The total quantity of aureomycin administered was 15.25 grams orally and 800 mg. intramuscularly. The temperature reached normal 36 hours after beginning treatment. Decided improvement of the mental status was apparent on the

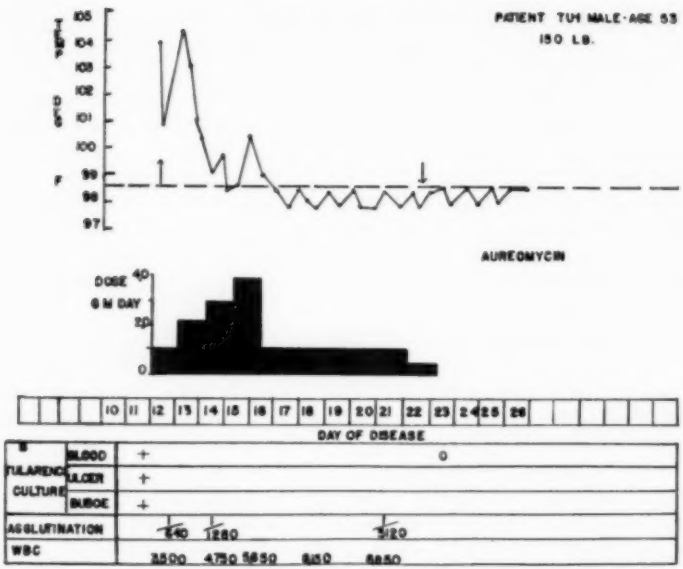


FIG. 7. *Case 1.* Tularemia. Aureomycin. Patient with ulcero-glandular type of tularemia complicated by pneumonia. Diagnosis confirmed by isolation of *B. tularense* from blood, ulcer and bubo. Rapid clinical and febrile response to aureomycin. (Reprinted from Jr. Am. Med. Assoc., 1949, cxxxix, 830.)

second day, and on the ninth post-treatment day a roentgenogram revealed practically complete clearing of the pulmonary infiltration. Bacteria identified as *B. tularense* were isolated from the lesion on the finger, from the epitrochlear gland and from the blood. The titer of agglutinins for *B. tularense* rose to 1/5120.

4. Discussion:

Results with the use of streptomycin in human tularemia are well known to be highly specific. In 56 patients Berson et al. [22] report that clinical improvement is observed within 48 hours after instituting therapy with streptomycin, and the mean time for attaining normal temperature was seven days. In 67 patients reported by Keefer et al. [23] there were 63 recoveries and four fatalities. In 55 the results were regarded as striking and immediate. Two relapses occurred in this series. In patients with tularemia treated with streptomycin by others the temperature returned to normal in periods ranging from two to six days. *B. tularense* have been found to disappear from the sputum and pleural fluid soon after administration of streptomycin. [24]

The fatality rate of tularemia complicated by pneumonia has been estimated to be as high as 30 per cent. Each of the three patients here reported manifested this complication. The patient with the ulcero-glandular type of tularemia would undoubtedly have died without chemotherapeutic help.

His rapid recovery is attributed to aureomycin. The ease of administration of aureomycin and its apparent freedom from toxic complications justifies a further clinical comparison with streptomycin in tularemia.

Rickettsial Infections

1. Chloromycetin: The efficacy of chloromycetin as a chemotherapeutic agent in experimental rickettsial infections was first demonstrated by Smadel and Jackson. [3] Results obtained with the use of this antibiotic in embryonated eggs and mice experimentally infected with the agents of scrub typhus, epidemic typhus, murine typhus, Rocky Mountain spotted fever and rickettsial pox indicated high specificity of action. An excellent chemotherapeutic effect was obtained in mice when administration of drug was delayed for 10 days after infection. Smith et al. [4] concluded from chick embryo testing that chloromycetin gram per gram was more effective against *R. prowazeki* (epidemic typhus) than streptomycin, para-aminobenzoic acid or methylene blue.

2. Aureomycin: The anti-rickettsial action of aureomycin was demonstrated in experimental infections of embryonated eggs, mice and guinea pigs against the agents of murine typhus, epidemic typhus, Rocky Mountain spotted fever, Q fever, rickettsial pox and scrub typhus by Wong and Cox. [9] No in vitro activity was demonstrated. Regardless of the length of time fever had been apparent in guinea pigs infected with Rocky Mountain spotted fever, epidemic typhus and Q fever, the animals were in most instances rendered afebrile within 48 to 72 hours by a single daily subcutaneous injection of 5 to 6 mg. of aureomycin/kilo for three to five days. [9] It has been shown that injection of a massive dose of infectious material into guinea pigs if followed by aureomycin treatment before symptoms appear, results in no signs of illness in the animal, but antibodies in measurable degree are induced and the animals become immune to subsequent challenge. If guinea pigs receive small doses of infectious material and then are treated with aureomycin before symptoms appear, neither fever nor other signs of illness develop, but antibodies do not always appear and the animals are often susceptible on rechallenge.

Therapeutic Results in Human Infections

1. Scrub typhus:

a. Chloromycetin: The highly efficacious results obtained in the treatment of 25 cases of scrub typhus have been reported. [17] The mean day for beginning treatment after the onset of illness was 6.2 and the mean duration of fever after beginning specific therapy was 31 hours. A reduction of the toxic state was observed to antedate the return of temperature to normal in all instances. The typical response of a patient with scrub typhus following treatment with chloromycetin is illustrated by Case 33 whose findings are graphically presented in figure 8. Rickettsiemia was demonstrated in 20 of

the 25 patients by animal inoculation and a positive Weil-Felix reaction was demonstrated in 24. All patients received an initial dose of approximately 50 mg./kilo and were subsequently given 0.2 to 0.3 gm. of drug by mouth every two to four hours for a variable period of time. The duration of treatment was eventually shortened to cover a 24 hour period as seen in the case illustrated below. Patients received about 6 grams of chloromycetin during this short period of therapy, and the uniform prompt clinical response to this short course of therapy further attests to the highly specific effect which chloromycetin exerts in this rickettsial disease. Relapses in the naturally occurring disease were not observed. This series of patients has now been extended to a total of 69. [25]

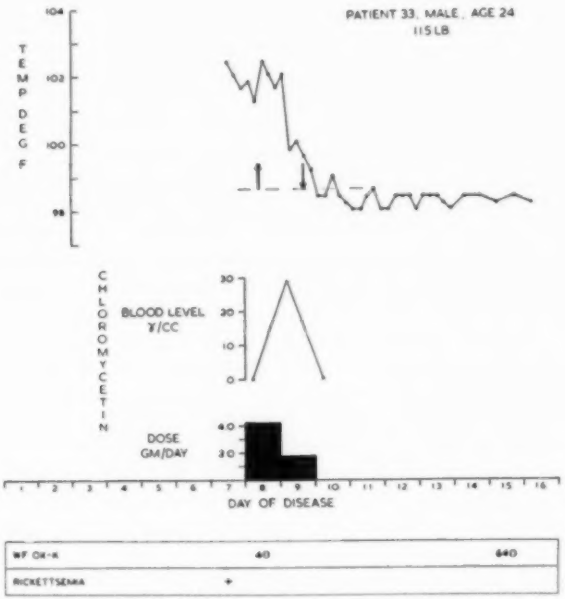


FIG. 8. *Case 33.* Scrub typhus. Chloromycetin. Course of scrub typhus (Tsutsugamushi disease) in a 24 year old patient who received chloromycetin for only 11 doses at 2 hourly intervals. Toxemia was rapidly reduced and the convalescence was uneventful. (Courtesy U. S. Army Scrub Typhus Team.)

b. Aureomycin: Similar results with aureomycin have been obtained by the U. S. Army scrub typhus team. [26]

2. Epidemic typhus:

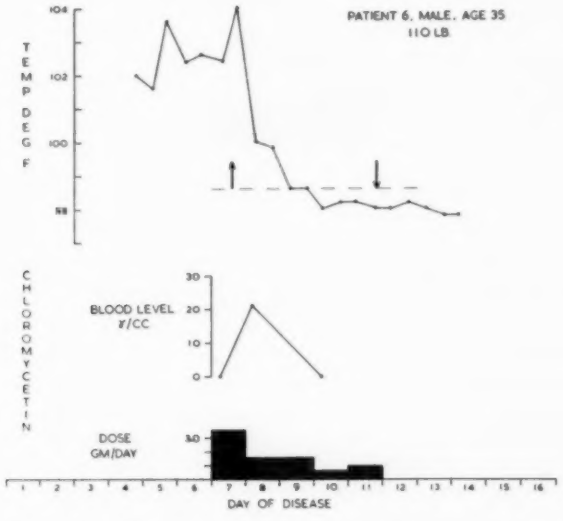
a. Chloromycetin: Smadel and his associates [27] administered crystalline chloromycetin orally to five patients with epidemic typhus fever in Mexico. The clinical diagnosis in all was confirmed by the demonstration of rising

titers for Proteus OX 19 agglutinins, rickettsial agglutinins and complement fixing antibodies. Two of the adult patients in this small series appear to have been very favorably benefited by chloromycetin. The response in one patient appeared equivocal, perhaps because of the small doses of antibiotic employed. Two children with mild epidemic typhus were apparently benefited by this therapy. Payne [28] in a series of 22 typhus patients treated with chloromycetin reports prompt reduction of toxemia in critically ill patients.

b. Aureomycin: No patients reported.

3. Murine typhus:

a. Chloromycetin: Ley and his collaborators [29] treated three murine typhus patients with chloromycetin. Laboratory confirmation of the clinical diagnosis in each instance was by demonstration of increasing titers of complement fixing antibodies and rickettsial agglutinins utilizing murine typhus antigens. Proteus OX 19 agglutinins were also present. Mean values for duration of illness prior to beginning treatment was 8.7 days and duration of fever after beginning specific therapy 53 hours. Dosage schedules are com-



WF OX-19		128	512
WF OX-K		40	40
RICK AGGLN	MURINE	160	640
	EPIDEMIC	0	80

FIG. 9. *Case 6.* Murine typhus. Chloromycetin. Patient with murine typhus given chloromycetin on the seventh day of illness. Prompt amelioration of headache and reduction of temperature. Convalescence rapid. (Courtesy U. S. Army Scrub Typhus Team.)

parable to those used in scrub typhus. Three patients do not permit statements of any statistical significance pertaining to therapeutic effectiveness. Nevertheless, the course of illness graphically represented in one case (figure 9) coincides in general with the pattern of response observed in scrub typhus and other rickettsial infections.

b. Aureomycin: A patient with murine typhus (figure 10) was diagnosed and treated by Dr. William Schulze of Greenville, South Carolina. The patient, a 45 year old woman, experienced continuous fever and a body rash was observed on about the eighth day of illness. Aureomycin was started on the tenth day of illness with 0.5 gram orally every four hours for two days and 0.5 gram every six hours for a total of 5.5 days of therapy.

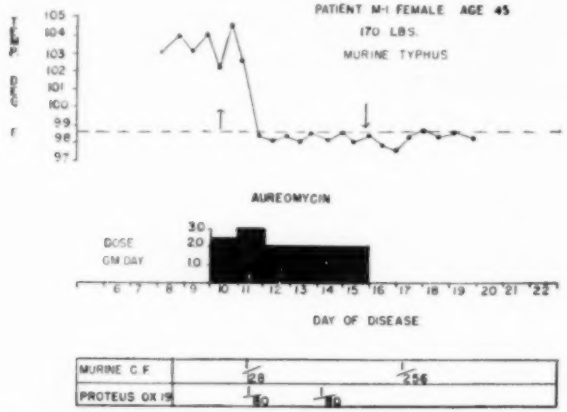


FIG. 10. *Case 1.* Murine typhus. Aureomycin. Rapid defervescence in patient with murine typhus who received aureomycin late in illness.

The temperature, plateau-like at 103° to 104° F. at the time of beginning treatment, descended by rapid lysis and became normal 36 hours later. The symptoms rapidly subsided and convalescence was uneventful. Complement fixing antibodies for murine typhus were 1/128 on the twelfth day of illness and 1/256 on the eighteenth day. The Weil-Felix titer was positive at 1/80. In a discussion of the aureomycin treatment of Rocky Mountain spotted fever,[33] Hill stated that he treated eight murine typhus patients with this antibiotic and reported the period of prostration reduced by about five to six days, as compared with cases on supportive therapy alone. The temperature returned to near normal in three days.

Discussion:

Based upon the meager clinical evidence available it appears that both chloromycetin and aureomycin exert specific benefit in murine typhus. The clinical response in this benign rickettsial disease is similar to that observed

in other members of the group. It is not possible to distinguish between the efficacy of either agent in the small series of cases reported.

4. Rocky Mountain spotted fever:

a. Chloromycetin: A study by Pincoffs et al. [30] describes the results obtained in the treatment of Rocky Mountain spotted fever with chloromycetin. Fifteen authenticated patients comprise this series of treated patients. A history of exposure to ticks was present in all, fever had been continuous from the day of onset, a rash was uniformly present, and secondary clinical features commonly observed in this disease such as headache, mental dullness, delirium and tarsal conjunctivitis were commonly observed. The diagnosis was confirmed in each instance by the presence of one or more of the following: (1) isolation of rickettsiae in guinea pigs, (2) agglutinating titers for proteus OX 19 of 1/160 or higher and (3) complement fixing antibodies in rising titer. Clinical improvement shown by the abatement of headache, mental dullness, etc., was definite within 24 hours of therapy. By the third day the patients were plainly convalescent. The average duration of fever after initiation of specific therapy was 2.2 days. Evidences of any toxic effect of the drug were not observed. The febrile response to treatment is typified in figure 11.

Effect of chloromycetin used late in illness: A 22 year old white male not included in the above series illustrates the favorable influence which chloromycetin exerts when used late in illness. The patient was seen in the Arlington, Virginia, hospital through the kindness of Dr. P. Swartz. On the eleventh day of illness the patient presented

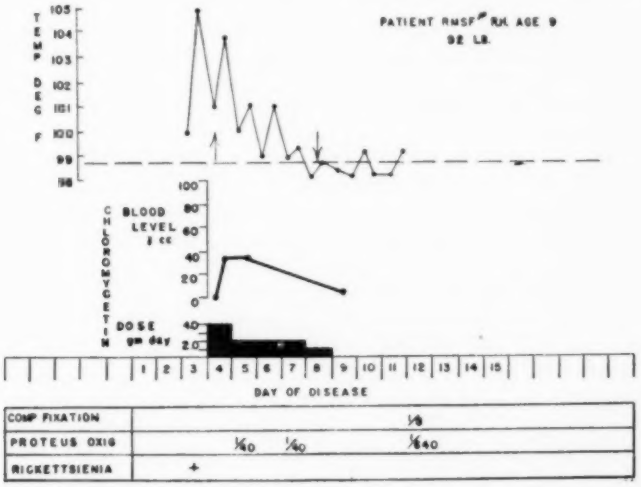


FIG. 11. *Case R. H.* Rocky Mountain spotted fever. Chloromycetin. A nine year old boy treated with chloromycetin on the fourth day of illness. Convalescence uneventful. Diagnosis confirmed by isolation of rickettsiae in guinea pig.

features indicating an extremely poor prognosis. Toxicity and dehydration were extreme, the temperature was 105° F., pulse was 140, respirations 40, and blood pressure 100/70. A macular rash was present, purplish red in color, extending principally over the hands, feet, forearms, legs, and to a lesser extent over the trunk. The patient was semi-comatose. Nuchal rigidity was present. On the eleventh day of illness 4 grams of chloromycetin were given as an initial dose, followed by 0.25 gram every two hours. By slow lysis the temperature reached and remained normal 2.5 days after instituting treatment. During this time there occurred dramatic improvement of the patient's general condition with fading of the rash and gradual improvement of the sensorium. Recovery was thereafter uneventful. The titer for Proteus OX 19 reached 1/1280, and the complement fixing antibodies were 1/256.

b. Aureomycin: Fortunately comparable series of patients with Rocky Mountain spotted fever treated with aureomycin are available. Thirteen patients fulfilling the clinical and laboratory criteria outlined above were treated by Ross et al. [31] in various clinics in Maryland and the District of Columbia.

Dosage: An initial loading dose of aureomycin was employed, administered on the basis of 2 to 5 mg./kilo at hourly and two hourly intervals during the active stages, changing to four hour intervals when the temperature reached normal. The average amount of aureomycin administered per patient was 9.5 grams given for a mean period of six days. The authors state that the optimum dose has not been determined.

Results: The rash disappeared within three to five days after the initiation of drug therapy in patients treated within the first four days of disease. The temperature subsided rapidly within an average of 2.3 days. Striking clinical improvement was likewise observed. Toxic manifestations other than nausea and vomiting were not encountered. Cooke [32] describes an additional patient treated on the fourth day of illness whose temperature reached normal 48 hours after institution of aureomycin treatment. Harrell's [33] results in three additional patients are similar.

Discussion:

The demonstrated efficacy of PABA (para-aminobenzoic acid) in Rocky Mountain spotted fever and other rickettsial infections has been shown. Toxicity is reduced and the temperature reaches normal after beginning this therapy in periods ranging from six days in one series of 17 patients [37] to three in a similar series. [38] On the other hand, PABA must be administered in very large doses, the blood electrolyte status must be closely evaluated and after prolonged administration the agent may be hepatoxic. [39]

Chloromycetin and aureomycin apparently obviate these undesirable traits of PABA with the possible exception of aureomycin which causes slight nausea. Each of these antibiotics, however, exerts a more rapidly favorable influence on the course of Rocky Mountain spotted fever than does PABA. With the evidence available one cannot distinguish between the relative efficacy of either antibiotic at the present time.

5. Q Fever:

Published accounts relative to the treatment of human cases are limited

to aureomycin. Lennette [40] and his coworkers treated 19 patients in California. The duration of fever was selected as the best objective criterion for the evaluation of the therapeutic effect of the drug. Individuals 26 years or older were chosen for treatment because this group had been shown to have a long and stormy course. In 10 patients treated during the acute phase fever continued for an average of 3.0 days after beginning therapy. Symptomatic improvement was noted within 48 hours. Two relapses occurred attributed by the authors to a suppressive rather than bactericidal effect of the antibiotic on the infecting agent.

Viral-like Infections

Experimental: Both aureomycin and chloromycetin show marked therapeutic effect in mice which have been infected intraperitoneally or intracerebrally with the agents of psittacosis and lymphogranuloma venereum. [3, 9] Results obtained by these investigators in embryonated eggs infected with these agents are essentially identical. It is to be emphasized that neither chloromycetin nor aureomycin has shown therapeutic activity against other experimental virus infections. [2, 9]

Therapeutic results in human viral infections:

1. Lymphogranuloma venereum:

a. Aureomycin: Wright et al. [41] report 25 cases of lymphogranuloma venereum treated with aureomycin. Eight of these patients with buboes showed decided reduction in size of the node at the end of four days treatment and elementary bodies were observed to disappear from the glands within one week of treatment. Three patients with proctitis showed prompt and decided improvement, whereas 14 patients with rectal stricture appeared to show only amelioration of the rectal pain, discharge and bleeding. The dosage of aureomycin was small, ranging from 10 to 40 mg. per day, administered intramuscularly.

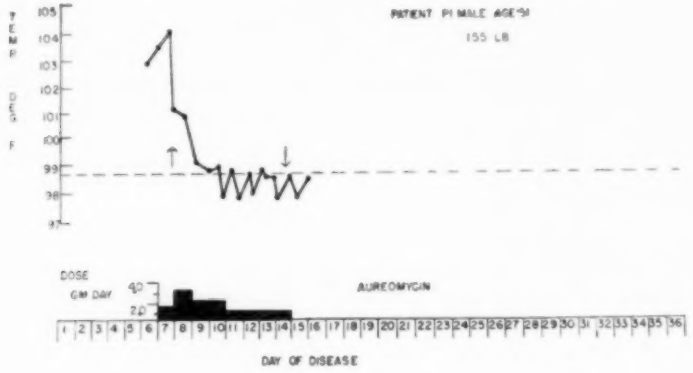
b. Chloromycetin: We have administered chloromycetin to one patient [42] with lymphogranuloma venereum of the glandular type without proctitis. The bubo decreased appreciably in size within five days of treatment, and elementary bodies were observed to disappear from the enlarged gland as determined by animal inoculation and by direct examination of prepared smears. The diagnosis in the patient was confirmed by isolation of the elementary bodies in mouse brain and by complement fixation tests.

2. Psittacosis:

a. Aureomycin: One patient with ornithosis [42] made a dramatic response to aureomycin. The patient received aureomycin on the seventh day of illness, and the response to treatment was immediate as indicated in figure 12. The disease was characterized principally by a bilateral pneumonitis and severe headache. Proof of diagnosis was by demonstration of complement fixing antibodies in the titer of 1/128. One week prior to onset of illness the patient had trapped 80 pigeons in the rafters of his barn.

3. Primary atypical pneumonia:

Primary atypical pneumonia is generally recognized as a clinical entity. The viral-like agent causing this disease has been successfully transmitted to normal human subjects. [43] A similar pneumonitis has been observed in diseases with specific etiology, such as influenza, psittacosis, ornithosis, tularemia, and the rickettsial diseases, particularly Q fever. Thus, in a study of atypical pneumonia a specific diagnosis must be searched for. There are now three independent series of patients treated with aureomycin in whom the diagnostic possibilities mentioned above have been considered. Schoenbach and Bryer, [44] Finland et al. [45] and Kneeland et al. [46] report the success-



W. B. C.	10,650	9400	7650	
COLD AGGLUTININS		0	0	0
PSITTACOSIS C.F.		1/16	1/16	1/20
Q-FEVER C.F.		0	0	0

FIG. 12. *Case P. 1.* Ornithosis. Aureomycin. Course of illness in patient with ornithosis. Infection acquired from pigeons and characterized by moderately severe pneumonitis and toxemia. Convalescence rapid and uneventful.

ful treatment of primary atypical pneumonia with this antibiotic. It was universally observed by these three groups of observers that the fever and symptoms began to improve promptly after beginning specific treatment and the temperature was normal usually within 48 hours.

Our results in the treatment of atypical pneumonia of non-specific etiology are confined to three patients. Two cases treated with aureomycin made a recovery very similar to that observed in the reported cases. One patient with the typical roentgen evidence of this condition responded equally favorably after the use of chloromycetin. It is of interest to point out that as a result of the screening routine which we have adopted for the diagnosis of

pneumonitis we were successful in finding the specific etiology of ornithosis in one instance and of tularemia in another.

Discussion:

The clinical experience with these antibiotic agents in viral-like infections is limited largely to the effect of aureomycin in the psittacosis-lymphogranuloma group and in primary atypical pneumonia of unknown etiology. Aureomycin has favorably influenced the course of the glandular and proctitis forms of lymphogranuloma venereum. Chloromycetin appears to have exerted similar effect in one instance. Ornithosis, a disease caused by an agent antigenically related to the lymphogranuloma virus has responded to aureomycin. Statements pertaining to the relative efficacy of aureomycin and chloromycetin in the psittacosis-lymphogranuloma group of human infections are not possible.

Aureomycin has very favorably reduced the course of disease in primary atypical pneumonia. It appears from the observations in one patient, that chloromycetin will share in this effectiveness.

Summary and Conclusions

In summary we feel that incontrovertible evidence is now available which places the two new streptomyces derived antibiotics, chloromycetin and aureomycin, on a level of therapeutic effectiveness comparable with penicillin. Both of these new antibiotics have been shown to be therapeutically effective after oral administration. Except for moderate gastrointestinal irritation resulting from aureomycin, significant toxic effects have not been observed. It is too optimistic to presume that untoward side effects will not be observed after the antibiotics are more extensively employed.

Chloromycetin and aureomycin have further extended the range of specific therapy to include the rickettsial and certain virus-like agents of disease. The results obtained in the treatment of patients with Rocky Mountain spotted fever, scrub typhus and murine typhus are highly specific and similar. Chloromycetin has been found effective in epidemic typhus fever whereas aureomycin has proved of great benefit to patients with Q fever. The results of further clinical trials are awaited. Aureomycin has enjoyed more extensive clinical use in the psittacosis-lymphogranuloma venereum group of diseases. It has demonstrated benefit in patients with lymphogranuloma-venereum and in human ornithosis. Chloromycetin treatment of one patient with lymphogranuloma venereum produced similar favorable results. Primary atypical pneumonia, a disease of suspected virus etiology, responds favorably to aureomycin. One patient treated with chloromycetin responded similarly.

Important diseases of the gram-negative group have been therapeutically controlled. Chloromycetin is unequivocally the drug of choice in typhoid fever. Both chloromycetin and aureomycin appear to be equally effective in brucellosis. Patients with tularemia have responded to aureomycin in a

manner comparable to streptomycin. Experimental results in mice infected with *B. tularense* show chloromycetin to be less effective.

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PANCREATIC LITHIASIS AND GASTRITIS (CASES WITH GASTROSCOPIC OBSERVATIONS) *

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PANCREATIC lithiasis was considered a rare disease and only a few cases were published before 1925. Recently the number of case reports has increased considerably, a fact due to the routine use of roentgenograms and to a greater interest in pancreatic pathology. A mere addition of case reports would seem superfluous. However, in two cases recently observed, it became possible to perform a gastroscopic examination, and in both cases the same type of change was found, namely chronic superficial gastritis. The gastroscopic diagnosis of superficial gastritis is reliable. When microscopic checks of the gastroscopic pictures become possible (Schindler [48]) identical characteristic pictures are found, the chief features of which are edema beneath the surface epithelium, plasma cell infiltration and extravasation of blood. Although chronic superficial gastritis is not rare (it is found in about 11 per cent of all patients with stomach symptoms), its occurrence in two cases of such a rare disease as pancreatic lithiasis can hardly be coincidental. Therefore, this observation calls for a reconsideration of the connection between pancreatic lithiasis and other gastrointestinal disease.

CASE REPORTS

Case 1. A 62 year old white male was seen first on February 28, 1945. He complained of weight loss of 40 pounds, diarrhea and intermittent suprapubic abdominal cramps of one year's duration. He had six or seven bowel movements a day, the stools being of mushy consistency. The patient also gave a history of diabetes, which was observed first in 1933. This was well controlled by insulin.

The patient had lived in the tropics for many years and gave a history of malaria, which had been successfully treated. Otherwise, he had been in perfect health. He did not drink, and smoked less than 15 cigarettes a day.

The *physical examination* revealed a well developed, poorly nourished white man. The abdomen was soft, not tender, no masses were palpated.

Laboratory tests. The urine did not contain albumin, indican or increased amounts of urobilinogen. Sugar was present when patient was off insulin. The blood count was normal; the sedimentation rate, 12; non-protein nitrogen 30 mg. per cent. From March to July, 1946, the blood glucose ranged between 83 and 230 mg. per cent. Amylase 4 Wohlgemuth units (normal 15 to 32).

Stool. After three days on Schmidt's test diet the stool looked mushy and yellow. Microscopically true creatorrhea was present. Enormous amounts of undigested striated muscle fibers were seen. Some material giving a positive reaction with Lugol solution was present. The fat was not definitely increased (no quantitative tests were undertaken, however).

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Duodenal juice. Its study for enzymes had the following results:

	10 min.	20 min.	40 min.	60 min.
Proteinase	.05 U	.75 U	.7 U	.81 U
Amylase	.3 U	.7 U	1.3 U	1.3 U
Lipase	.8 U	1.5 U	2.1 U	2.4 U

These figures indicate complete absence of enzymes and severe pancreatic dysfunction.

Roentgen-ray examination. An upper gastrointestinal series was undertaken on February 2, 1945. At fluoroscopy there were rather coarse folds visible in the upper portion of the stomach. However, no definite pathology was seen. Films revealed a round, sharply limited, dense 12 mm. radiopaque shadow at the right side of the first lumbar vertebra surrounded by other much smaller irregular shadows (figure 1). *The larger shadow was located within the duodenal loop* (figure 2). On subsequent scout films it was demonstrated again. In lying position the upper border of the shadow was level with the upper border of the second lumbar vertebra. In upright position the shadow had shifted down, its upper border being level with the upper edge of the third lumbar vertebra, a shift of 2 cm. A barium enema was given on March 5, 1945. No organic pathology of the colon was found. On June 12, 1945 a roentgen-ray study of the gall-bladder was undertaken. The gall-bladder was faintly filled. The round shadow was found 3 cm. to its left.

FIG. 1. Calcification in head of pancreas (Case 1). Roentgen-ray compression spot film. The round stone shadow lies in the center of the picture. Stomach and duodenum are filled with barium, the duodenum points downward. (Pylorus at 12 o'clock, cap of duodenum at 10 o'clock, descending portion of duodenum at 5 o'clock.)

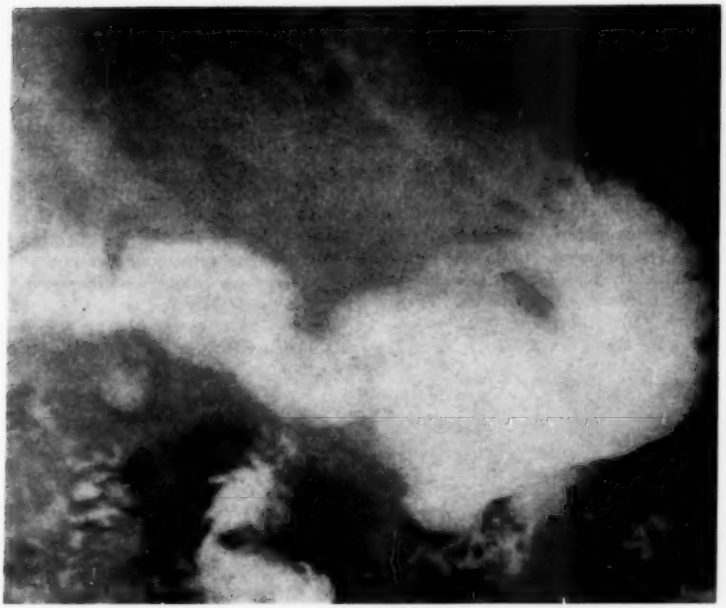

FIG. 2. Calcification of head of pancreas (Case 1). Roentgen-ray survey. The location of the stone shadow within the duodenal loop is demonstrated.

Sigmoidoscopy (March 10, 1945) revealed no pathology.

Gastroscopy (March 12, 1945). The mucosa of the antrum was normal. In the body, especially in the upper anterior wall, membranes of adherent mucus were visible. No atrophy was seen. The gastroscopic impression was that of chronic superficial gastritis of the body of the stomach.

Electrocardiogram showed a left axis deviation.

Because of the roentgen-ray pictures, the stool findings, the low blood amylase, the absence of the pancreatic enzymes of the duodenal juice, and of the case history of diabetes of long duration, the diagnosis of *pancreatic lithiasis* was made.

Large amounts of pancreatic enzymes (3 × daily 4 Stamyl tablets) were given together with 60 units of insulin daily. *The diarrhea stopped promptly*, the patient gained four pounds in two months and the test stool showed only moderate amounts of undigested muscle fibers. The suprapubic cramp-like pain continued, however.

On June 6, 1945, an exploratory laparotomy was done by Dr. Eugene Joergenson at White Memorial Hospital, Los Angeles. Through a transverse upper abdominal incision the abdomen was opened and explored. An unusually thick wall of the entire colon, most marked in the sigmoid, was found. The liver and gall-bladder were normal; there were a number of adhesions. The stomach was normal. The duodenum was somewhat dilated throughout. The head of the pancreas was one and one-half times normal size and stony hard in consistency, particularly along the posterior portion of the head. The gastrocolic ligament was opened and the body of the pancreas explored. The peritoneum over the pancreas was incised and the substance of the pancreas inspected. The pylorus was freed from the head of the pancreas.

After it was noted that the maximal density was on the posterior surface, a Kocher's mobilization of the duodenum was done by incising the lateral peritoneal reflection and rolling the duodenum with the head of the pancreas medially to a point where the superior mesenteric vessels cross the third portion of the duodenum. The pancreatic substance was then incised and with sharp and blunt dissection the point of incision carried down into the area of calcification. The maximum point of density in the head of the pancreas would not permit penetration of a needle. The calcification was found in connection with ramifications which extended into the parenchyma of the gland. No intraductal calculi were found. The stroma of the head of the pancreas was extremely dense, and it was impossible to divide its substance bluntly. Some of the calcareous material was removed and a biopsy from the head of the pancreas was taken. The pancreas substance was then sutured. The retro-duodenal pocket was drained and the incision was closed.

The *microscopic section* through the biopsy taken is pictured in figure 3. It is interesting that the pathologists—without knowledge of the case history—diagnosed "Adenocarcinoma Grade I." (Naturally the long case history and the fact that the

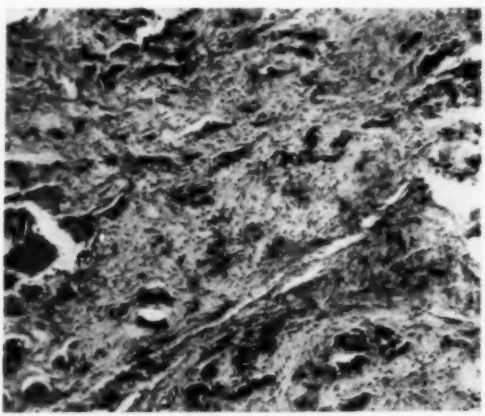

FIG. 3. Fibrosis of pancreas (Case 1). Photomicrograph, × 80. The entirely fibrotic gland contains only remnants of small ducts and of acini, which simulate carcinoma formation.

patient is alive three years later without weight loss excludes this diagnosis. It is well known that patients with carcinoma of the pancreas do not usually live longer than a six to seven month period.) The pancreas is entirely fibrotic, its glandular substance is completely destroyed and within the fibrous tissue remnants of ducts are found.

Because of the continuing suprapubic pain a urologic study was carried out on December 21, 1945 by Dr. D. Rosenbloom with negative result. Figure 4 shows the topographic relation of the pancreatic calcification to the right kidney pelvis.

The patient has continued to have attacks of suprapubic pains requiring narcotics. However, there has been no weight loss and no diarrhea. The patient is alive and is under substitutive therapy with enzymes and insulin. He continues to have considerable weakness.

Summary. A white male developed diabetes at the age of 50 years. In retrospect it must be assumed that this coincided with the onset of the chronic

pancreatitis, which later was complicated by extensive calcification. At the age of 61 weight loss and diarrhea developed. Suprapubic abdominal pain was present. Typical roentgen-ray pictures, stool findings (creatorrhea), absence of enzymes in the duodenal juice and low blood amylase values led to the diagnosis of pancreatic lithiasis. At exploration no calculi of the ducts were found, but fibrosis of the entire pancreas with extensive calcification of its head. Microscopic examination of the biopsy showed that no functioning glandular tissue was left. Severe fibrosis was seen. Two additional unusual findings were present: (1) Unexplained thickening of the mus-

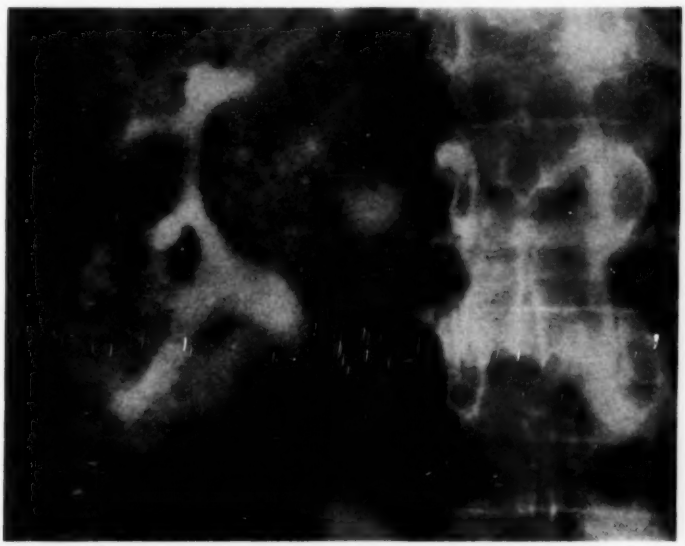

FIG. 4. Positional relation of calcification of head of pancreas to right kidney (Case 1). Pyelogram. The right kidney pelvis is filled with radiopaque material. The large stone is seen medially. In this film many smaller concrements lateral to the large stone are visible.

culature of the colon, especially of the sigmoid, which probably was responsible for the suprapubic pain of the patient. (2) At gastroscopy marked chronic superficial gastritis was found. It will be discussed later. Under substitution therapy the patient gained weight and lost the diarrhea. He is alive, though weak, after three years.

Case 2. A 30 year old white male was referred to us on January 24, 1946 by Dr. Eugene Fischer of Glendale, California. He complained of two different symptoms. (1) Several years ago diabetes was found which was only partly controlled by insulin. (2) Since October 1945 he had observed "oily" stools which were passed with great amounts of gas from five to six times a day. He had no pain. His appetite was very good. He had lost some weight, but regained it. Four years ago a laparotomy was carried out because of terrific pain in the right upper quadrant.

The patient smoked two and a half packages of cigarettes a day, and did not drink. He was not nervous. Lately he had observed diminution of his sexual potency which worried him.

The physical examination revealed a very well nourished man. No abnormalities were noted in the abdomen. General examination revealed no pathological findings.

Laboratory examination. Blood count normal. Sedimentation rate: 15. Glucose: 156 mg. per cent. Blood amylase (Somogyi method), 60 units (normal 80 to 150). Stool did not contain occult blood after meat free diet. After Schmidt's test diet the stool was unformed, containing large amounts of grossly visible fat and residues of potatoes. Microscopically great amounts of striated muscle fibers were seen. Many potato cells were present. After addition of Lugol solution large amounts of Lugol stained material, free and in cells, were observed. The amount of fat was much increased. Biliary drainage was not possible.

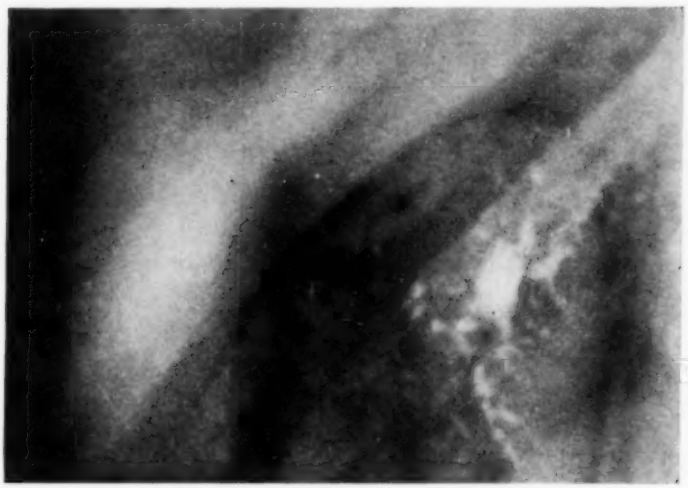

FIG. 5. Positional relation of pancreatic calculi to the gall-bladder (Case 2). Cholecystogram.

Roentgen-ray examination (February 3, 1946). At fluoroscopy the stomach was a high lying steerhorn type with smooth contours, but folds could not be well demonstrated. The stomach after three and one-half hours was one-third filled, after 24 hours emptied. A cholecystogram showed the gall-bladder well filled. Between its shadow and the spine over the twelfth rib, numerous calcified areas were seen, of varied size and shape and many irregular ramifications (figure 5).

Gastrointestinal series. Within the loops of the duodenum the same calcifications were seen and further calcified specks were observed in the region of the twelfth rib. This was repeatedly checked by flat films. The right-left sided calcifications were constantly present.

Gastroscopy was done on February 8, 1946. The entire stomach was well seen and the pylorus was observed. The gastric mucosa looked everywhere moist and edematous, "watery." In the lower depths adherent mucus was seen. The gastroscopic impression was that of chronic superficial gastritis.

Further follow-up was not feasible, but the patient was reported alive and working one year later.

Summary. In a 30 year old white male the diagnosis of pancreatic lithiasis was made from characteristic roentgen-ray pictures, together with the history of diabetes, the observation of characteristic pancreatic stools, and low amylase in the blood. The patient had had only one severe pain attack four years ago, for which laparotomy was undertaken. There is little doubt that this pain was due to the pancreatic lithiasis. Remarkable was the good nutritional condition of the patient even before enzyme preparations were given.

Discussion

Lionello [25] recorded *232* cases of pancreatic lithiasis up to 1944. From the literature 90 more cases were collected [6, 8, 12, 13, 14, 18, 25, 28, 31, 32, 34, 38, 45, 54, 55, 59, 61] bringing the total cases to 324 (including our two cases).

Pathology. It is difficult to decide whether the stone formation antecedes or follows fibrotic inflammation. Probably both possibilities occur. Our first case is a proved case of calcification, and since diabetes was observed very early, long before other serious dysfunction of the gland occurred, it seems likely that a primary fibrotic inflammation led to secondary calcification. The early appearance of diabetes in the second case might lead to a similar interpretation. Yet, the evidence is not conclusive.

Etiology. The coincidence of two cases of stone formation within the pancreas with chronic superficial gastritis should cause reconsideration of the rather vague and speculative ideas about the etiology of pancreatic lithiasis. If two diseases are found together, always four possibilities must be considered, which for our cases may be formulated as follows: (1) The two diseases may have no relationship with each other; (2) stone formation and pancreatitis are primary, causing secondary superficial gastritis; (3) superficial gastritis is the primary disease, leading to secondary lithiasis and pancreatitis; (4) both diseases are due to a common etiologic agent.

(1) The probability of the coincidental occurrence of superficial gastritis with a very rare disease such as pancreatic lithiasis in two subsequent cases is almost nil.

(2) Since within the alimentary tract the pancreas lies beyond the stomach and the pancreatic juice usually does not enter the stomach, infection of the stomach from the pancreas is not likely. We know of no case in which the bacterial origin of chronic superficial gastritis has been proved. The stomach is a sterile organ and its acid juice destroys invading microorganisms quickly. It is true that *uncontrolled* reflux of intestinal juice such as occurs in postoperative stomachs, may lead to extremely severe superficial gastritis. However, gastroscopic observation in our second case proved that the pyloric sphincter rhythm was a normally regular one.

(3) It seems much more likely that the inflamed stomach could produce secondary inflammation of the pancreas with stone formation. In chronic

superficial gastritis transitory anacidity is frequent (Schindler[49]), the stomach then is no longer sterile. Its often abundant bacterial flora may irritate the mucosa of the duodenum and small intestine, leading to chronic inflammation. This inflammation could reach the pancreas. It is true that under normal circumstances the valve-like folds of the ampulla of Vater prevent the regurgitation of the duodenal juice into the pancreatic duct, and the passage of pancreatic juice has a cleaning effect. However, in abnormal conditions such as inflammation of the intestinal mucosa with patency of the stoma of the duct, infection of the pancreatic duct may occur.

(4) Is there any common etiologic cause for superficial gastritis and pancreatic lithiasis? Two possibilities may be considered. It has been speculated that all forms of chronic gastritis may occasionally be due to some kind of focal infection. Similarly focal infection may lead to secondary pancreatitis and stone formation. However, as far as gastritis is concerned, this theory has never been proved conclusively. In our two cases no hidden focus of infection was discovered.

Much more worthy of consideration is the second possibility, namely that both diseases are due to a vitamin A deficiency. Atrophic gastritis has been proved to be a deficiency disease in many instances. Superficial and atrophic gastritis, however, form a disease entity, superficial gastritis often preceding atrophic gastritis. Etiological factors proved to be important in atrophic gastritis may conceivably be contributory also in the origin of superficial gastritis. Atrophic gastritis (which often is due to a deficiency state) may develop in deficiency of Castle's factor, of iron, of vitamin B and, according to Blomquist, also of vitamin A (compare for these questions the chapter on etiology of chronic gastritis in the monograph by one of us, R. S.[49]). Some cases of atrophic gastritis react definitely to the administration of very large doses of vitamin A. The close relationship between vitamin A and the integrity of epithelium is well known. Lack of vitamin A leads for instance in the cornea to degeneration of the epithelium to subsequent inflammation and to the picture of xerophthalmia. On the other hand vitamin A deficiency may lead to stone formation after desquamation of epithelium. This has been proved especially for kidney stones.[15, 20, 28, 37, 59]

It seems that in animals having a diet low in vitamin A there is a tendency to inflammation and stone formation in the urinary tract. The same may be true of the pancreas. Vitamin A deficiency may cause desquamation of the epithelium of the pancreatic ducts with the subsequent infection and inflammation. The cellular desquamated elements may form the fibrillar network (Robson and Cammidge[45]), which would form a nucleus for calcium deposition. This would be favored by the alkaline reaction of the pancreatic secretion.

Anderson[3] was the first author to consider vitamin A in the etiology of pancreas disease. In several cases of fibrocystic disease of the pancreas he observed bronchiectasis with desquamation of the bronchial epithelium, probably due to vitamin A deficiency.

Vitamin A deficiency may well be considered as the common cause of chronic superficial gastritis and of pancreatic calculus.

Symptoms and Diagnosis

From the observation of our cases it becomes evident that a triad of signs strongly suggests the presence of pancreatic lithiasis: (1) History of diabetes; (2) diarrhea, the stools showing microscopically the signs of pancreatic dysfunction, especially creatorrhea; (3) roentgen-ray picture revealing calcification in the region of the pancreas. Symptoms which may or may not be present are pain, weight loss (in spite of good appetite) and weakness, nausea and vomiting. Additional objective findings are the lack or diminution of enzymes in the duodenal contents and a decrease of amylase in the blood.

Like many other diseases pancreatic lithiasis may be asymptomatic for varying periods, or constantly.

The *diabetes* in our two cases anteceded for a long period of time the onset of other symptoms referable to the pancreas.

Diarrhea. The gross and microscopic examination of the stool is of great importance. It yields typical pictures.

Roentgen-Ray Examination. If together with diabetes and pancreatic diarrhea radiopaque shadows in the pancreas region are found, the diagnosis of pancreas stone is simple. If one or the other two symptoms is missing, the radiologic differential diagnosis may be difficult. In one of our cases the roentgenologist, not knowing the case history, considered the radiopaque shadow seen as barium-filled diverticulum of the small intestine or as gall stone.

The high contents of the calcium in the pancreatic concretions make their demonstration in the film easy. They may be discovered in the scout film. The stones usually have an irregular outline, being only rarely faceted. They are found most frequently in the region of the head of the pancreas, limited above by the upper border of the first lumbar vertebra and below by the lower level of the third lumbar vertebra.

The differential diagnosis from gall stones, kidney stones and calcified lymph nodes may become necessary. If there are multiple shadows spread over the entire pancreas, as in our case 2, no doubt about their nature will arise. If there is only a solitary shadow in the region of the head, the differential diagnosis may be difficult. If ramifications of calcium surround the medial density pancreas stone is almost certain although calcified lymph nodes may give similar pictures. Gall stones, if radiopaque, possess only some layers consisting of calcium bilirubinate or calcium carbonate. The stone then will present concentric rings, the so-called Liesegang rings, occasionally with a central point of calcification. If the patient is turned into the lateral position, gall stones and pancreas stones will be found in the front of the spine, while kidney stones and calcified nodes are in the plane of the vertebral column or are cast behind it.

Capurro and co-workers,[6] utilizing scout films, studied the variations of the position of the radiopaque shadows with the patients in lying and in upright positions. With the patients standing kidney stones may be dislocated two to four centimeters downwards and gall stones five centimeters downwards if the stone is in the neck; eight to 10 centimeters, if the stone is in the fundus of the gall-bladder. Calcified nodes and parietal calcification however, do not change their location. As described previously pancreatic calculi may move down two centimeters when the patient is put in upright position. This phenomenon, if present, excludes calcified nodes.

Cholecystography and pyelography may show the opaque shadows within or without the gall-bladder or the kidney respectively. Of great value for the recognition of one shadow as pancreas stone is its demonstration within the duodenal loop. This is done best by introducing a duodenal tube into the duodenum and then taking a film. The same relationship can be demonstrated by a simple upper gastrointestinal tract series. This is shown in our figures 1 and 2. The positional relationship of the same stone to the kidney pelvis is shown in figure 4. The positional relationship of multiple calculi of our case 2 to the gall-bladder shows on figure 5.

The other signs have been described by many authors and their recapitulation appears unnecessary.

Treatment

It certainly is interesting that patients with almost complete lack of pancreatic function may not only live, but even be in good nutritional condition (see our case 2), if only the diabetes is treated sufficiently. It seems that even total pancreatectomy is feasible without endangering life, if the function of the islet apparatus is substituted. It seems that rather small amounts of insulin are needed. Yet, it is advisable to substitute the external pancreatic secretion also by giving large amounts of pancreatic enzymes orally and in some cases it may even be necessary. That such substitution therapy is effective has been proved (Schindler,[49] Schmidt, Beazell, Crittenden and Ivy[52]). Brunschwig[4] believes that survival for many months is possible without pancreatic juice in the small bowel. In a personal letter to the authors, Whipple[64] wrote: ". . . in our series of some 40 radical pancreaticoduodenectomies we noted a marked difference in the need for pancreatic enzymes. This was true duct occlusion. In our . . . cases of total pancreatectomy, one did not need panteric tablets, the other did. . . . In general, I believe that the administration of pancreatic enzymes for the first few weeks is advisable. Withdrawal of this therapy can be gradual and complete if tolerated." In our case 1 the diarrhea stopped and the amount of muscle fibers in the stool diminished considerably after administration of large amounts of pancreatic enzymes. Therefore we believe that this type of therapy should be tried in every case. In our first case the number of muscle fibers in the feces after test diet diminished considerably after substitutive

therapy. Snell and Comfort [53, 54] recommended administration of lipocaic or other lipotrophic substances to avoid fatty degeneration of the liver.

Concomitant gastritis, enteritis or gall-bladder disease should be treated adequately.

Two indications for surgery may exist. Removal of a duct stone may not only eliminate pain attacks, but also stop progressive destruction and fibrosis of the gland. The mortality of this operation is, according to Walters and Claggett,[62] surprisingly low. All their patients recovered. Of 22 patients reported by Seeger [55] in 1925 in whom stones were removed only two died.

If the pancreatic function is destroyed surgery may still be undertaken for overwhelming pain attacks. Pancreatectomy may be considered. Details about this procedure will be found in Whipple's [65] paper. Rienhoff and Baker [44] recommended vagotomy for pain referable to the pancreas.

Summary

1. In two cases of pancreatic lithiasis gastroscopy was done and revealed chronic superficial gastritis in both. The possible relationship of the two diseases is discussed in this paper.

2. A triad of signs may suggest presence of pancreatic lithiasis: history of diabetes, diarrheic stools showing the signs of pancreatic dysfunction, and roentgenograms revealing calcification in the region of the pancreas.

3. Some patients with complete destruction of the pancreatic function may live under insulin, but without substitution of the outer pancreatic secretion by enzymes. Others require—or are benefited by—enzyme treatment.

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PENICILLIN AND PENICILLIN-MALARIA IN THE TREATMENT OF TABES DORSALIS *

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The demonstration of favorable results with the use of penicillin in the treatment of tabes dorsalis, shortly after the introduction of this drug in the treatment of syphilis, was of special interest, in view of the highly complex and uncertain origin of the clinical manifestations of this disease. Stokes et al.[1] reported in 1944 that improvement in lightning pains following treatment with penicillin occurred in four of seven patients with this symptom. Subsequently Gammon et al.[2] reporting on a larger series, found that 66 per cent of tabetic patients with abnormal spinal fluids showed improvement in spinal fluid following penicillin therapy, compared to 88 per cent improvement in patients with dementia paralytica. No data on clinical improvement were reported. O'Leary et al.[3] were disappointed with the results of penicillin therapy in tabes, observing no improvement in ataxia, crises, and bladder symptoms. Only 15 per cent of their tabetic patients with leg pains showed improvement. In a later study based upon more extensive follow-up, Stokes et al.[4] observed definite clinical improvement in 31 per cent of tabetics, compared to similar improvement in 30 per cent of cases of dementia paralytica, using improvable symptoms as a criterion for the former group. Improvement in lightning pains was particularly notable, and a higher proportion of patients with tabes showed normal or near-normal spinal fluids at the end of treatment than was observed in patients with dementia paralytica. More recently Koteen[5] has also obtained favorable results in tabes dorsalis with penicillin alone.

These studies are of interest not only from a therapeutic standpoint, but also in throwing some light upon the nature of the pathogenesis of the signs and symptoms of tabes. It is difficult to conceive of an effect by penicillin other than upon an inflammatory process in producing these favorable results. These results are of significance in view of the doubt which has been cast by some workers upon the relationship of an inflammatory process in the nervous system to the genesis of the clinical manifestations of this disease.

In a previous paper[6] an analysis of the results of treating a group of 46 dementia paralytica patients with penicillin alone and with penicillin-malaria was made, and it was found that the results with penicillin alone equaled those achieved by the use of penicillin combined with malaria. The com-

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parison was based upon changes observed in spinal fluid, clinical manifestations, and in relapses occurring following a period of improvement. In the present paper a similar type of investigation has been directed toward a group of 30 patients with tabes dorsalis, all of whom have been followed for at least six months after therapy. The purpose again will be to assess the relative merits of penicillin alone and penicillin combined with malaria. This appraisal is more difficult than in the case of dementia paralytica, since tabes is a more slowly progressive and less dramatic disease than dementia paralytica. Many of the clinical manifestations of tabes which respond to treatment are subjective in nature, and spontaneous remission of some of these manifestations, such as gastric crises, is known to occur. It is acknowledged that such remission may be the result of factors other than the specific treatment administered, thereby necessitating long periods of follow-up before conclusions may be drawn with reference to permanent improvement in such manifestations. Nevertheless, a remission in symptoms, complete or partial, even for a period of six months is of definite significance, particularly in the case of the more severe manifestations of tabes. A further difficulty in evaluating therapy in tabes is that many patients present themselves for treatment with irreversible manifestations in the presence of an "inactive" (Dattner-Thomas concept) spinal fluid. There has been some difference of opinion as to whether therapy may be expected to accomplish anything for patients of this type. It appeared worthwhile therefore to compare the results of treatment in patients showing active and inactive spinal fluids, to see whether any difference could be noted in the effect upon clinical manifestations.

While it would be highly desirable, in comparing two forms of treatment in tabes, to make such a comparison in groups resembling each other with respect to signs and symptoms, their duration, previous treatment received, and other variable factors, it is impossible from a practical standpoint to do so, in view of the long incubation period of tabes, and the variable background of patients presenting themselves for treatment. The best that can be done is to indicate the effect of treatment upon signs and symptoms which are known to be influenced favorably by treatment, for the groups under consideration.

Clinical Material

Thirty patients with tabes dorsalis are included in this study. Half of these received penicillin alone, while the remainder received combined penicillin-malaria therapy. Of the 15 patients in each treatment group, three in the penicillin group and four in the penicillin-malaria group were negro, the remainder being white. The duration of symptoms of tabes for these groups is indicated in table 1. It will be observed that the average duration of symptoms was longer for the penicillin-malaria group than for the penicillin group, eight patients in the former group having had symptoms for four years or more whereas none in the penicillin group had symptoms exceeding four years in duration.

With regard to previous treatment received, both groups resembled each other more closely. Table 2 indicates the time the last treatment was received prior to the present course of treatment, and table 3 indicates the type of treatment received by both groups. It will be seen that eight patients in each group had not received treatment within a year or more of the present treatment. Four patients in the penicillin group and five in the penicillin-malaria group had received no previous treatment. Previous treatment was essentially similar in character for both groups.

TABLE I

Duration of Symptoms

	Penicillin	Penicillin-Malaria
Less than 1 year	3	2
1–3 years	12	5
4–5 years	0	2
Over 5 years	0	6
Total	15	15

TABLE II

Time Relationship of Previous Treatment to Present Treatment

Treatment Received	Penicillin	Penicillin-Malaria
Up to admission	2	2
Previous 6 months	4	3
6–12 months ago	1	2
13–24 months ago	4	2
Over 24 months ago	0	1
None	4	5
Total	15	15

TABLE III

Nature of Previous Treatment Received

	Penicillin	Penicillin-Malaria
Routine	7	6
Tryparsamide	2	2
Penicillin	1	1
Fever therapy	1	1
None	4	5
Total	15	15

TREATMENT SCHEDULES

Fifteen patients received penicillin alone, in the form of the sodium salt in doses of 30,000 units every three hours day and night. Fifteen other patients received a combination of penicillin plus malaria therapy, in a manner so that penicillin was given throughout the febrile course. The average number of hours of fever above 103° F. (rectal) was 47. The amounts of penicillin given to patients in both groups are indicated in table 4. It will

TABLE IV

Amount of Penicillin Administered

Million Units	Penicillin	Penicillin-Malaria
3.0–4.0	3	6
5.0–6.0	4	5
7.2–8.0	7	3
10.0	1	1
Total patients	15	15
Mean amount of penicillin	6.2	5.25

be seen that the average amount of penicillin given to the group receiving penicillin alone was somewhat higher (6.2 million units) than that administered to the penicillin-malaria group (5.25 million units).

RESULTS OF TREATMENT

The results of the course of treatment given to each group will be evaluated upon the basis of improvement in spinal fluid and in improvable clinical manifestations. The observation periods upon which these results are based are indicated in table 5. It will be noted that seven patients in the penicillin group and seven in the penicillin-malaria group were under observation for over two years following treatment.

As might be expected, a certain proportion of patients in each group showed normal, or "inactive," spinal fluids on admission, in spite of definite tabetic manifestations. Table 6 indicates spinal fluid cell counts before and

TABLE V

Observation Period Following Treatment

	Penicillin	Penicillin-Malaria
6–12 months	5	7
13–24 months	3	1
25–36 months	5	3
Over 36 months	2	4
Total	15	15

TABLE VI

Changes in Spinal Fluid Cell Count Following Treatment

Cell Count	Before Treatment		After Treatment		After 3 Months		After 6 Months	
	P*	P-M**	P	P-M	P	P-M	P	P-M
Below 5	6	5	10	7	10	9	13	9
5–9	1	2	4	5	1	1	1	2
10 or above	8	8	1	3	1	1	0	1
Not done	0	0	0	0	3	4	1	3
Total	15	15	15	15	15	15	15	15

* P = Penicillin.
** P-M = Penicillin-Malaria.

after treatment for both groups, for the period of six months during which most change occurred. It will be observed that before treatment eight patients in each group had cell counts above 8 per cu. mm., and that nine patients in the penicillin group and 10 in the penicillin-malaria group had cell counts above four. If only those patients with cell counts above four per cu. mm. to start with are considered, all patients in the penicillin group (8) and six of nine patients in the penicillin-malaria group (one not done at the end of six months) achieved cell counts of four or less at the end of six months. The penicillin group therefore made a somewhat better showing with reference to spinal fluid cell count response.

TABLE VII

Changes in Spinal Fluid Protein Following Treatment

Protein (mg.)	Before Treatment		After Treatment		After 3 Months		After 6 Months	
	P	P-M	P	P-M	P	P-M	P	P-M
Below 30	0	2	2	0	0	2	2	5
30–40	3	2	1	7	5	5	7	3
41–50	5	4	6	5	4	1	3	3
Above 50	7	7	6	3	3	3	2	2
Not done	0	0	0	0	3	4	1	2
Total	15	15	15	15	15	15	15	15

With regard to spinal fluid protein, table 7 shows that 12 patients in the penicillin group and 11 in the penicillin-malaria group showed values above 40 mg. per cent (normal limit for method employed) before treatment. Six months after treatment seven of the former group and five of the latter group showed spinal fluid protein values below 40 mg. Return to normal was therefore slower than in the case of the cell count, and was essentially similar for both groups.

TABLE VIII

Changes in Spinal Fluid Kolmer Titer Following Treatment

Spinal Fluid (c.c.)	Before Treatment		After Treatment		After 3 Months		After 6 Months	
	P	P-M	P	P-M	P	P-M	P	P-M
.03	4	3	1	1	0	0	0	1
.06	3	4	2	0	1	1	0	1
.125	2	1	6	6	1	2	2	4
.25	2	4	2	3	5	3	6	3
.5	2	1	1	3	1	2	2	1
1.0	1	0	1	1	2	2	2	1
Negative	1	2	1	1	2	1	2	2
Not done	0	0	1	0	3	4	1	2
Total	15	15	15	15	15	15	15	15

Table 8 shows changes in spinal fluid Kolmer titer for both groups. It will be observed that whereas nine patients in the penicillin group and eight in the penicillin-malaria group showed positive tests with 0.125 c.c. or less spinal fluid before treatment, at the end of six months only two of the penicillin group (one not tested) and six of the penicillin-malaria group (two not tested) still remained in this category. The response of the spinal fluid Kolmer reaction was therefore less favorable in the latter group. Changes in blood Wassermann titer showed no relationship to those observed in spinal fluid, and will not be discussed in detail.

TABLE IX

Improvement in Clinical Manifestations Following Treatment

	Total		Improvement									
			Worse		None		Slight		Moderate		Marked	
	P	P-M	P	P-M	P	P-M	P	P-M	P	P-M	P	P-M
Pains	9	13							4	4	5	9
Paresthesias	9	10							3	5	6	5
Gastric crises	1	4							1	4		
Ataxia	8	12			1		3	4	4	8		
Bladder symptoms	5	5			1		1	3	3	2		
Optic atrophy	4	6	1				3	6				
Sexual impotence	2	2					2	2				

Turning now to a consideration of improvement observed in clinical manifestations in both groups following treatment, table 9 lists the important improvable clinical manifestations observed in both groups and their response to treatment. Signs commonly present in tabes dorsalis which do not change with treatment are not included. The order of listing of signs and symptoms shows decreasing response to treatment. Thus, pains and paresthesias responded best, whereas sexual impotence and optic atrophy showed least improvement. However, for the latter condition, arrest of progress should be considered as a satisfactory response. The response to both forms of treatment shows no striking superiority of either method. All patients with pains or paresthesias in both groups showed moderate to marked improvement. With penicillin the relief of pains was somewhat slower than in the case of penicillin-malaria, but at the end of three months appeared to catch up with the latter in achievement. Slight to moderate improvement in ataxia, sexual potency, and in bladder symptoms was observed in an equivalent proportion of patients in both groups. Of three patients in the penicillin group and four in the penicillin-malaria group with progressive optic atrophy, all showed arrest of progress of the process, with the exception of one patient with rapidly progressive optic atrophy in the penicillin group who went on to blindness in spite of 7.2 million units of penicillin. Due to the

presence of only a single patient with gastric crises in the penicillin group, conclusions cannot be drawn with respect to the effect of penicillin alone upon this symptom, although moderate improvement was observed in this instance. One patient with extremely severe gastric crises, not included in this study, failed to show much improvement following the administration of penicillin alone, but obtained marked relief following penicillin-malaria.

Of interest is the fact that patients with "inactive" spinal fluids (spinal fluid cell count of four or less) showed improvement comparable to that observed in patients with elevated cell counts. Of six patients in the penicillin group with inactive fluids, all except one showed moderate to marked improvement in clinical manifestations. Five patients with inactive fluids in the penicillin-malaria group likewise showed moderate to marked improvement in clinical manifestations. The improvement observed in these patients with inactive fluids was observed for the most part in pains and paresthesias. Four patients with inactive spinal fluids in each treatment group showed moderate to marked improvement in pains or paresthesias or both.

A single patient, in the penicillin group, showed a recurrence of symptoms following a period of improvement. This patient had a recurrence of tabetic pains two years after treatment which provided complete relief. The only significant change in the spinal fluid at the time of the clinical relapse was an elevation of the spinal fluid protein. Even this single relapse indicates the long follow-up period required for evaluation of permanent results in tabes dorsalis, although a period of freedom from symptoms of such duration should probably be recognized as a favorable result of treatment.

For the range of penicillin dosage employed in our patients, no difference in results was observed which could be related to lower or higher dosage of penicillin. The same may be said with regard to duration of symptoms of tabes before treatment. Seven patients with duration of symptoms of five years or more showed marked improvement in these symptoms following treatment with penicillin-malaria.

Discussion

Patients with tabes dorsalis constitute an older age group than is seen in other forms of neurosyphilis, due to the longer average period required for the development of this form of neurosyphilis. For this reason such patients are frequently a poor risk for fever therapy. Such therapy has nevertheless been used, in spite of its hazards, due to the severity of certain tabetic symptoms and their frequent amelioration by fever therapy. A form of treatment which would be less rigorous and more widely applicable under conditions which preclude fever therapy would be highly desirable, particularly if its effectiveness approached that of malaria therapy. This study has endeavored to ascertain whether penicillin holds promise of serving as a satisfactory substitute for malaria therapy.

Under the conditions of our study, and within the limitations of the follow-up period over which patients were observed, the results with penicillin alone compared favorably with those observed following combined penicillin-malaria therapy, for most symptoms of an improvable character. Pains and paresthesias led among the symptoms showing comparable and satisfactory response to both forms of therapy. Due to the presence of a single patient with gastric crises in the penicillin group, the effect upon this symptom cannot be evaluated, although the result was satisfactory in this instance. It is probable that penicillin-malaria offers more prospect of relief for cases of a severe nature, which do not respond to penicillin alone. With the exception of one case of rapidly progressive optic atrophy, arrest of the progress of optic atrophy by penicillin compared favorably with that of penicillin-malaria. It may well be that in rapidly progressive cases of this condition every possible therapeutic weapon should be employed, of which the best would appear to be a combination of penicillin and malaria. In cases showing less rapid progression penicillin alone may be justified, at least as preliminary therapy. Such manifestations as ataxia, bladder symptoms, and sexual impotence showed comparatively less, but equivalent response, with both regimens of treatment.

The improvement observed in certain tabetic symptoms in patients with inactive spinal fluids before treatment indicates that treatment should not be withheld in the absence of evidence of activity in the spinal fluid. Apparently symptoms of tabes in the presence of a normal spinal fluid cell count do not necessarily predicate refractoriness to treatment. This observation encourages speculation as to whether the inflammatory process which is so favorably influenced by penicillin might not reside outside the central nervous system.

It should be kept in mind that during the period of the above study, penicillin was a changing mixture of variable potency. That it produced the results which it did for a group of symptoms known to be resistant to ordinary therapy augers well for its future rôle in tabes dorsalis, particularly as therapeutically more effective penicillins, such as crystalline penicillin G, become more widely used. For those patients unable to tolerate malaria therapy, at least, penicillin promises to be a great boon. Further study is needed to determine to what extent it is justifiable to withhold malaria therapy in favor of penicillin alone. On the basis of our experience to date, penicillin alone appears to provide amelioration of many of the clinical manifestations of tabes comparable to that observed with combined penicillin-malaria therapy.

Conclusion

1. An analysis is presented of the results of therapy in 30 patients with tabes dorsalis, half of whom were given penicillin alone and the remainder penicillin-malaria.

2. Approximately two-thirds of the patients in each group showed "active" (Dattner-Thomas) spinal fluids before treatment.

3. The effect upon spinal fluid and improvable clinical manifestations in both groups failed to demonstrate any marked superiority of penicillin-malaria over penicillin alone, for the period of observation, and with few exceptions.

4. For rapidly progressive optic atrophy and for severe cases of gastric crises, combined penicillin-malaria probably offers most in the way of treatment.

5. For the other clinical manifestations of tabes dorsalis penicillin alone appears to offer results approaching those achieved by penicillin-malaria. Penicillin alone is justified as preliminary therapy, at least, for such manifestations.

6. For the dosage range of penicillin employed, no difference was observed in results between lower and higher dosage.

7. Marked amelioration of symptoms was observed following penicillin-malaria even in patients with duration of symptoms of five years or more.

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SECONDARY AMYLOIDOSIS *

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Slightly more than 100 years ago, Rokitansky [1] described a disease in which the organs were infiltrated by a firm, waxy, homogeneous material. Since then, a large volume of literature has concerned itself with this disease process. Early writers, notably Wilks,[2] included other conditions, then not understood, under the general category of lardaceous disease. This condition was also called "bacony" or "waxy" degeneration. Virchow [3] observed that the infiltrating material in lardaceous disease becomes blue-black on the application of iodine followed by dilute sulfuric acid. Because of this similarity to vegetable starch, he suggested that the substance be called "amyloid."

It was early recognized that long-standing suppurative disease of bone and pulmonary or osseous tuberculosis were frequently associated with this disease. Wilks [2] noted in 1856 that amyloidosis was occasionally associated with chronic syphilis, and he suggested its occurrence in patients with "rheumatism." It has been seen in patients with malignant tumors, rheumatoid arthritis, chronic ulcerative colitis, subacute bacterial endocarditis, leukemia, multiple myeloma and other diseases.[4-7] Amyloid has been reported to occur in about one fourth of subjects dying of tuberculosis. The pathogenesis of amyloidosis is not yet established.

It is not the purpose of this report to review extensively the literature on secondary amyloidosis.

Primary systemic amyloidosis is a form of the disease in which no preexisting illness is present and in which the material is often deposited prominently in the heart and other mesodermal structures. Most observers believe that the amyloidosis associated with multiple myeloma should be classified separately, because it usually resembles the primary type in distribution of lesions. Localized collections of amyloid which simulate neoplasms are a third type of the disease.

The organs usually involved most severely in the common secondary variety of amyloidosis are the spleen, liver, kidneys and adrenals. Involvement of the gastrointestinal tract, lymph nodes and pancreas is not uncommon.[8] The thyroid [9] and other organs are more unusual sites of amyloid deposition.

It was noted by Virchow [8] that renal amyloidosis was important clinically, and he stated that in some cases "Bright's disease" was due to infiltration of the glomeruli with this substance, with resultant renal insufficiency.

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It has become generally recognized that the nephrotic syndrome or uremia may be produced by this disease.[10] In most examples of secondary amyloidosis there is involvement of the spleen. The spleen may be markedly enlarged and is characteristically pale and firm. The degree of involvement of the liver is extremely variable although in most cases amyloid is found in this organ, and in some, great hepatomegaly occurs.[11] The adrenal glands, particularly their cortical portions, are involved in most instances.[12] They become larger than normal, the size increasing as the degree of infiltration increases.

Most observers agree with Ziegler[13] that the amyloid is laid down primarily in the connective tissue of the various organs affected. Even in early times, it was recognized that the deposition of this substance in the walls of small blood vessels occurred among the muscle fibers of the media. Peters[14] has pointed out that the amyloid is laid down first on and around the cells of involved organs.

The Present Study

Etiologic Factors. Of 44 cases of amyloidosis encountered at necropsy at the Mayo Clinic during the 25 year period ending December 31, 1946, 30 were of the secondary type. Seven were examples of primary systemic amyloidosis, three were associated with multiple myeloma, in three there was minimal infiltration localized to the heart and one was an example of an amyloid tumor below the tracheal bifurcation. The etiologic diseases in the series of cases of secondary amyloidosis are given in table 1.

Table I

Etiologic Diseases in Secondary Amyloidosis

Disease	Cases
Tuberculosis	7
Carcinoma	5
Osteomyelitis, multiple	3
Infections of the urinary tract and fistulae	3
Pulmonary abscesses	2
Bronchiectasis	2
Rheumatoid arthritis	2
Hodgkin's disease	2
Chronic ulcerative colitis	2
Actinomycosis	1
Syphilis, tertiary	1
Total	30

In 40 per cent of the cases of secondary amyloidosis the disease was secondary to tuberculosis or carcinoma. In four of the cases the tuberculosis was pulmonary, in two it was of bone and in one it was peritoneal. In all seven instances, mild to severe secondary infection complicated the tuberculosis. In the five cases associated with carcinoma the primary sites were the bladder, colon, stomach, kidney and ovary; severe secondary in-

fection was present in three of these. Of the two patients with pulmonary abscess, one had an abscess of the brain and the other, abscesses of the liver. The patient with actinomycosis had multiple abdominal sinuses. One of the patients with Hodgkin's disease had, after radiation therapy, very little residual tumor but died with signs of renal and hepatic failure due to amyloidosis.

The age of the patients who had secondary amyloidosis at death appears to be merely a reflection of the age at which the various primary diseases occurred. The ages varied from four to 70 years, the average being 39 years. Nine patients were in the fourth decade.

Information of a reliable nature as to the duration of the inciting disease was present in 25 instances. The duration varied from 12 to 200 months. In only five cases was the primary disease of less than two years' duration. This is in agreement with the view that the "etiologic" disease is usually present at least two years before the onset of amyloidosis.

Clinical Signs. The signs of renal involvement were the most outstanding signs of amyloidosis in this series. Albuminuria was noted in 26 of the 27 cases in which the urine had been examined during the last six months of life. The albuminuria was graded from 1 to 4, 1 being the least, and 4 the most severe. The albuminuria was graded 4 in six cases, 3 in 10 cases, 2 in nine cases and only 1 in one case. Rather marked albuminuria, that is, grade 3 or 4, was present in 59 per cent of this group. This agrees closely with the findings reported by Altnow, Van Winkle and Cohen.[15] Edema was noted during the course of the disease in 11 of the total series of 30 cases, an incidence of 37 per cent. Severe uremia occurred in three cases.

Three patients had hepatic enlargement that was noted clinically, and one had icterus. Of interest is the fact that splenomegaly of clinical significance did not occur.

Intravenous Congo red tests were done in five of the 30 cases. The dose used was 0.2 c.c. of a 0.6 per cent solution of Congo red per kilogram of body weight. Two of those tested gave completely negative results and in the other three the disappearance of the dye from the blood varied from 40 to 75 per cent in one hour. If 90 per cent disappearance is considered [16] necessary for a diagnosis of amyloidosis, no positive results were obtained in this series. It should be noted that many of the patients with most marked involvement were not tested.

Pathologic Features. The percentage of cases in which each organ was affected is given in table 2.

Spleen. The spleen showed amyloid infiltration in every case. In three instances the involvement was diffuse, the so-called bacony spleen. In two of these there was slight, and in one moderate, diffuse deposition of amyloid throughout the organ in the splenic cords. In the other 27 cases the material was confined to the regions of the splenic follicles. In many of these the accumulations were grossly visible as small rounded, grayish, semitranslucent nodules giving the appearance of the sago spleen. Five of these 27

TABLE II

Percentage of Cases in Which Organs Were Involved in Secondary Amyloidosis

Organ	Per Cent
Spleen	100
Kidneys	93
Adrenal glands	93
Liver	87
Lymph nodes	68
Pancreas	63
Prostate (16 cases)	62
Thyroid	59
Gastrointestinal tract	55
Heart	43
Lung	10
Striate muscle	0

spleens showed amyloid nodules up to 3 mm. in diameter with some confluence of the nodules, and these were considered severely affected. Seventeen spleens contained amyloid masses averaging 1 to 2 mm. in diameter and these were considered moderately involved. The remaining five of the 27 spleens showed only minimal infiltration in the follicles. In all degrees of involvement the average splenic weights were only slightly greater than normal. The largest spleen weighed 567 gm., but it was only slightly affected by amyloidosis of the sago type. The site of deposition of the material in the sago spleens was in the splenic cords at the periphery of the lymph follicles in the cases in which the disease was mild (figure 1). It appeared that the follicles were crowded out and replaced by amyloid as the degree of involvement increased. Later the nodules expanded peripherally. In the majority of the spleens there was deposition of amyloid of a mild to moderate degree in the media of the small arteries and arterioles, but this could usually be seen with certainty only by employing special stains. In mild degrees of infiltration of the media of vessels the amyloid could be seen to encase individual smooth muscle cells as though the substance had been laid down on the surface of these cells. Splenic involvement was of no recognizable clinical significance in this series, although one of the commonly mentioned signs of amyloidosis is splenomegaly.

Kidneys. The kidneys were infiltrated with amyloid in 28 of the 30 cases. The glomeruli were involved in all 28 of these. Since the glomeruli are usually considered of primary importance in renal function, the amount of amyloid in them was used as the basis for estimation of the degree of kidney involvement. Mild degrees of involvement consisted of the deposition of only insignificant amounts of the material in the walls of the capillary tufts. Involvement was considered of severe degree when it was obvious that the blood flow through the glomeruli was markedly or completely obstructed by the amyloid in the tufts (figure 2). Those kidneys showing intermediate amounts of infiltration were labeled "moderately affected." On the basis of these criteria, the kidneys were classified on purely histologic grounds. Eight were considered to be severely, nine moderately and 11 mildly, involved.

In all of the examples of renal amyloid disease, except in a few in which slight infiltration occurred, there was amyloid in the media of the small blood vessels of the cortex and medulla and outside the endothelial cells of the capillaries throughout the kidneys. The amount of infiltration in the walls of the small vessels was, in all cases, very small. The amount of the material surrounding the capillaries was, in some instances, great. In those with little involvement of this latter type, the amyloid was obviously just outside the capillary endothelium, but with more extensive deposits, especially in the medulla, it was impossible to be certain whether the amyloid was

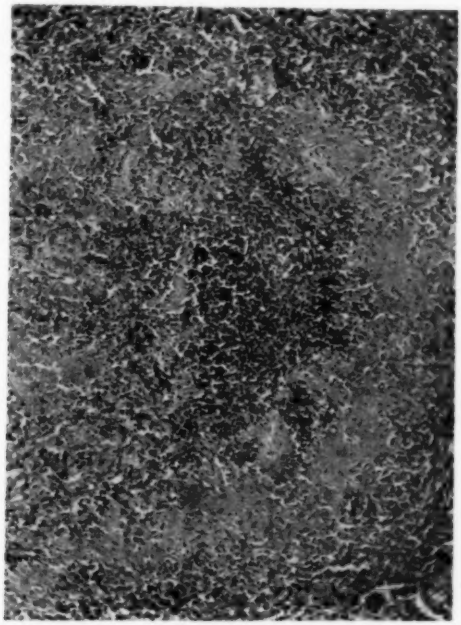

FIG. 1. Spleen with moderate sago deposit. Note involvement of periphery of follicle (hematoxylin and eosin × 85).

laid down primarily in relation to capillaries or to the basement membranes of tubules. In two of the cases of severe disease, the medullary tubules were considerably separated by the infiltrating amyloid.

Severely affected kidneys were firm and pale or contracted and looked like the kidneys of chronic glomerulonephritis (figure 2 *inset*). There was no appreciable difference in the average weights of the kidneys in the various degrees of involvement. It is noteworthy, however, that in the three patients who had marked uremia, the kidneys were small, the combined weights being 157, 158 and 160 gm. respectively. In these there was a con-

siderable number of hyaline glomeruli and glomeruli which contained amyloid that appeared to be changing into hyalin, as has been described by Noble and Major [17] and others. There was considerable tubular atrophy in these kidneys. The histologic appearance was consistent with the view that the tubules atrophy when the glomeruli become functionless, and the glomeruli finally assume a hyaline structure. This glomerular change is well demonstrated with the methyl violet and van Gieson stains. In all of the seven instances in which iodine was applied to the fresh gross specimens,

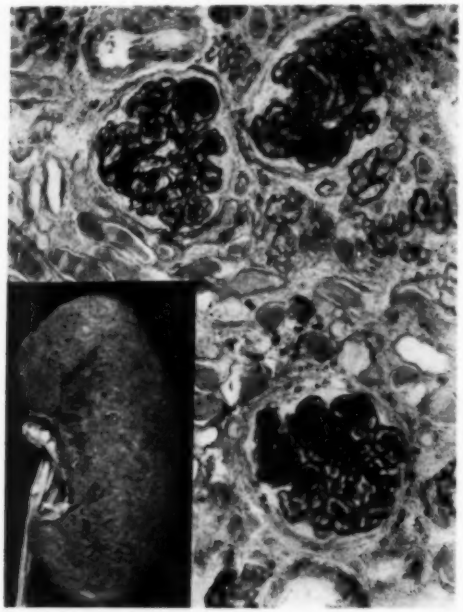

FIG. 2. Kidney severely affected by deposition of amyloid. Note amyloid deposits on the basement membranes of the glomerular capillaries and in the walls of some small arteries. Patient died of uremia (methyl violet stain; photographed by using B and H Wratten filters × 200). Inset. Gross appearance. Both kidneys weighed a total of 160 gm.

the results were positive for amyloid. In some, mahogany brown spots throughout the renal cortices clearly represented involved glomeruli.

Albuminuria was present in every case of renal amyloidosis in which studies of the urine had been done in the last six months of life. In 15 of these 25 cases, the albuminuria was graded 3 or 4. The degree of albuminuria paralleled closely the degree of renal glomerular amyloid infiltration.

Edema developed in 10 of the 28 cases of renal amyloidosis. Its occurrence, too, paralleled closely the estimated degree of renal involvement.

It was noted in six of the patients with severe amyloidosis of the kidneys, in three of those with moderate and in only one of those with mild amyloidosis of the kidneys.

Serum protein studies were made on six of the patients with edema. The total protein levels varied from 3.0 to 6.5 gm. per 100 c.c. and in four cases there was reversal of the albumin-globulin ratio. In three patients with edema and in two without edema, the serum protein levels were below 5 gm. The blood cholesterol level was 303 mg. per 100 c.c. in one and 315 mg. in the other of two patients whose serum protein levels were 3.7 gm. with reversed albumin-globulin ratios and edema. In one of these, the blood level of total fat was 980 mg. per 100 c.c. and the fatty acid level was 696 mg. Of two additional patients with serum protein levels below 5 gm. and reversed albumin-globulin ratios, one had edema and a blood cholesterol level of 130 mg. and the other had no edema and a blood cholesterol level of 235 mg. A definite nephrotic syndrome was present in four instances; two of these patients had severe and two had moderate renal amyloidosis.

The systolic blood pressure, expressed in millimeters of mercury, was more than 150 in only three of the patients. In an 18 year old male with uremia, the blood pressure was 194 systolic and 100 diastolic. This patient's glomeruli were severely affected, and the terminal blood urea level was 400 mg. per cent. In a 33 year old male with moderate renal amyloidosis but without uremia, the pressure was 200 systolic and 128 diastolic. The third patient, whose pressure was 175 systolic and 100 diastolic, was a 48 year old male with carcinoma of the colon, mild renal amyloidosis and a normal blood urea level.

Renal insufficiency of a severe degree occurred in three cases. In these three the blood urea levels rose to 346, 400, and 444 mg. per 100 c.c. respectively. Renal insufficiency of milder degree was apparently due to the amyloidosis in three others whose blood urea levels ranged between 48 and 96 mg. In three additional patients the blood urea levels rose to more than 100 mg. One of these patients, however, had pyelonephritis, the second had recently undergone nephrectomy and the third had adequate cause for prerenal azotemia. The blood urea level rose to 70 mg. in a patient whose left kidney was congenitally absent and who had metastatic carcinomatous lesions around the right kidney, and to 84 mg. in another who had peritoneal tuberculosis and multiple pelvic abscesses. In these last two cases only slight amounts of amyloid were present in the glomeruli and the azotemia was probably not on that basis. Of the three patients with most severe uremia, the kidneys in two were judged to be markedly, and in one moderately, infiltrated with amyloid. The kidneys in these were contracted, and there is no doubt that the azotemia was caused by amyloidosis.

Adrenal glands. The adrenal glands contained amyloid in 27 of the 29 cases in which material was available for study. In 12 instances, this involvement was slight, the condition being barely recognizable or the amyloid occurring in scattered tiny masses in the cortex. In four, the cortex was

almost completely replaced by amyloid and the disease was considered severe. In the remaining 11, moderate replacement of the adrenal cortices had occurred. In all cases the amyloid infiltration was in the adrenal cortex, the medulla being spared except for small amounts of the material in the walls of small blood vessels in some instances. In 19 cases, periadrenal vessels near the capsule were similarly affected. In these vessels, the amyloid was in the media. Small arteries and veins were both involved. In the adrenal cortex, the amyloid was deposited on the reticulum fibers between the sinusoids and the cords of cortical cells. This site of deposition was readily demonstrated by use of the combination of reticulum and methyl violet stains. With increasing amounts of amyloid, the cortical cells were compressed by the material and atrophy occurred. With minimal degrees of infiltration, the substance was found only in the zona fasciculata (figure 3). With moderate involvement, the zona reticularis also was often involved, and only in the severely affected glands was there an appreciable amount of amyloid in the zona glomerulosa. In no case was clinically significant Addison's disease present. It is admitted, however, that the debilitating primary diseases may have masked signs of adrenal cortical insufficiency.

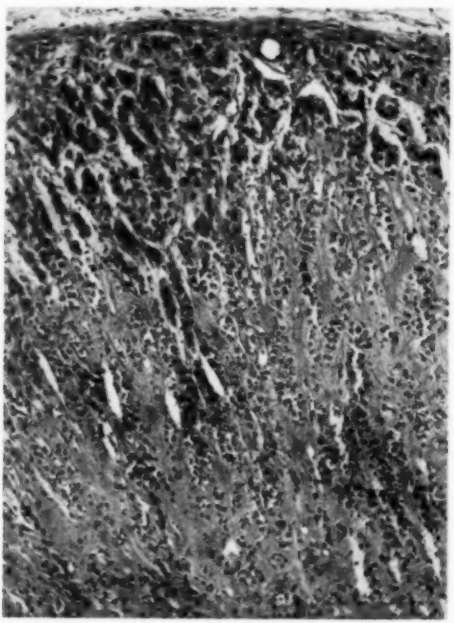

FIG. 3. Adrenal gland showing slight amyloid infiltration, chiefly in the zona fasciculata (hematoxylin and eosin × 85).

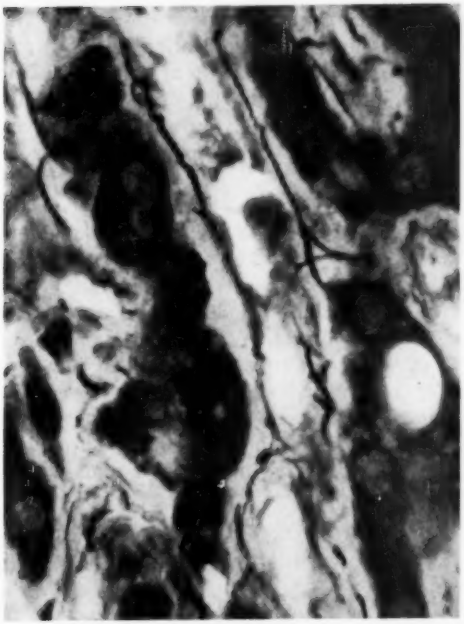

FIG. 4. Moderate amyloid infiltration of the liver. Note deposits on the reticulum between the sinusoids and the cords of hepatic cells (reticulum stain with methyl violet counterstain × 960).

Liver. Marked hepatic amyloidosis occurred in only one case. In this instance, multiple sections from the various lobes of the liver showed extensive replacement of parenchymal cells with the infiltrating material. The liver weighed 2,900 gm. and had been noted to be large clinically. In 26 of the 30 examples of secondary amyloidosis, the substance was found in the liver. In seven of these, it was present only in the media of the small arteries and veins of the portal triads, and in two, the vessel walls were moderately thickened and their lumina slightly narrowed. In some instances, the amount of amyloid was so minimal that special stains were necessary for its demonstration. In 13 cases, there was slight infiltration of the hepatic lobules with amyloid. In this location, the substance was deposited between the hepatic cords and the sinusoids. Sections stained for reticulum and then with methyl violet showed the material to be located on both sides of the reticulum fibers separating the sinusoids from the cords of hepatic cells (figure 4). In nearly every case in which the hepatic parenchyma contained amyloid, there was slight to moderate involvement of the small blood vessels of the liver. The evidence indicates that the earliest site of deposition of this substance in the liver is usually the media of small blood vessels,

which is in accord with the observation of Virchow. In five instances, there was a moderate degree of amyloid infiltration in the hepatic parenchyma. In most of the examples in which there was parenchymal amyloid the material was found predominantly at the periphery of the lobules, but in some the midzone of the lobules was chiefly involved. The average weights of the livers in which moderate, slight or no parenchymal deposition of amyloid occurred were about the same. Clinical hepatomegaly was noted in the patient with severe amyloidosis of the liver, in another with moderate infiltration and no record of weight of the liver available, and in a third in whom the liver was slightly infiltrated and weighed 2,140 gm.

Clinically important hepatic insufficiency was not seen except in one patient with slight to moderate amyloid infiltration of the liver. This patient had a direct serum bilirubin level of 0.7 mg. per 100 c.c. and showed grade 3 (24 to 40 per cent) retention of bromsulfalein in the blood one hour after the intravenous administration of 5 mg. of the dye per kilogram of body weight. Liver function tests were done in no other cases.

Lymph nodes. Amyloid was found in lymph nodes in 19 of the 28 cases in which nodes were available for study. Abdominal or thoracic nodes or

FIG. 5. Lymph node showing amyloid deposits and tuberculosis (hematoxylin and eosin × 150).

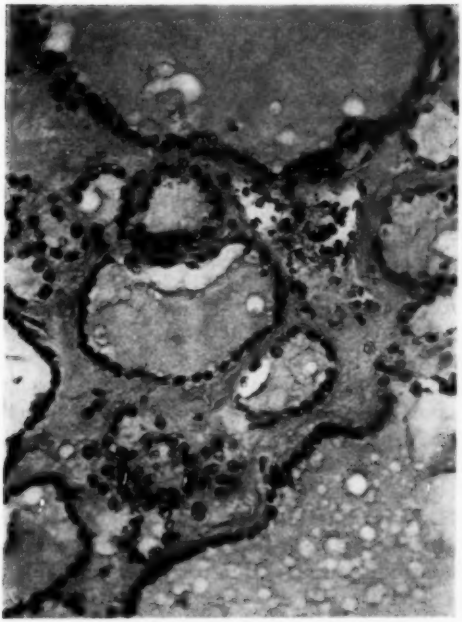

FIG. 6. Thyroid showing moderate amyloid deposition between the acini (hematoxylin and eosin × 235).

both were studied in these cases. In 12 of these, there was only slight infiltration in the form of minute masses of amyloid in clusters, usually near the capsule of the nodes (figure 5). These nodes were not grossly enlarged. In an additional seven cases there were somewhat larger clumps of the material in the nodes. These were considered moderately involved, but they, too, were not significantly altered in size. The walls of capillaries and small blood vessels within the nodes occasionally showed slight deposition of amyloid. Nodal involvement was not of clinical significance in this series.

Pancreas. Infiltration of the pancreas with amyloid was not outstanding although in 19 of the 30 cases some degree of infiltration occurred. Infiltration of the media of the small arteries and veins was noted in 17 cases and, in six of these, there appeared to be some slight resultant decrease in the size of the vascular lumina. In 10 of the cases, capillaries in the pancreatic interstitial tissue showed slight thickening of their walls due to amyloid. In three cases, there was slight involvement of the capillaries within the islets of Langerhans. In only two cases was there amyloid infiltration in the region of the basement membranes of the pancreatic acini,

and this was not excessive. No clinical signs could be attributed to pancreatic involvement.

Prostate. Prostatic tissue was available for examination in 16 of the 21 male patients. In 10 of these, there was slight amyloid infiltration of the media of small arteries and veins of the prostate. Special stains were necessary for demonstration of these deposits in some of the prostates. No other prostatic involvement was demonstrated.

Thyroid. Amyloid was demonstrated in the thyroid gland in 13 of the 22 cases in which tissue from this organ was available. In five of these, there was only slight infiltration in the walls of the small blood vessels. In four cases, there was minimal deposition of amyloid in the connective tissue among the thyroid acini. In four, this latter type of involvement was moderate in degree, there being definite separation of the acini by the homogeneous material (figure 6). In five cases in which amyloid was deposited in the interstitial tissue, there was associated mild involvement of the walls of small blood vessels. Clinical enlargement of this organ was not observed.

Gastrointestinal tract. Material from the stomach, small intestine or large intestine or all three was available for study in 27 of the 30 cases of secondary amyloidosis. Amyloid was found in some part of the gastrointestinal tract in 15 of these. In six cases, the infiltration was confined to the media of the small arteries and veins in the bowel wall, most commonly in the submucosa. In seven, there was minimal amyloid deposition in the mucosa, where the material appeared to lie in the walls of the capillaries. In some of these latter cases there was slight infiltration, with amyloid, of the muscularis mucosa and the muscularis propria where it was deposited on the surface of the individual smooth muscle fibers; also there was minimal deposition in the small blood vessels of the bowel wall. In two cases, the amyloid infiltration in the intestinal mucosa was considered to be of moderate degree. In these the material had replaced at least 50 per cent of the mucous membrane, and minimal deposition on the muscularis mucosa and muscularis propria had occurred. In one of these cases the patient had abdominal cramps and mild diarrhea during the last six weeks of life. Assuming that these symptoms were due to the amyloidosis, they were the only clinical manifestations of this phase of the disease.

Heart. The heart was affected in 13 of the 30 cases. This incidence is somewhat higher than would have been noted had not all hearts been stained with methyl violet. In several instances, the presence of amyloid had not been suspected after sections stained with hematoxylin and eosin had been studied. In none of the hearts was there any appreciable degree of amyloidosis. In five, small amounts of amyloid were found only in the media of small arteries and veins in the myocardium. In addition to this type of involvement, in eight cases there was minimal deposition of the substance on the reticulum surrounding heart muscle fibers. This latter type of deposition was patchy and easily demonstrated by the use of combined reticulum and methyl violet stains.

Other organs. In three cases, a very small amount of amyloid was found surrounding some of the capillaries of the pulmonary alveolar septa. In none of the 11 cases in which peripheral nerves were available for study was there any evidence of amyloid in the sections.

Comment

These 30 examples of secondary amyloidosis conform to the usual description of the disease in that the spleen, kidneys, adrenal glands and liver were found to be the organs most frequently involved. By careful study, including the use of special stains, small amounts of amyloid were found in a fairly high percentage of organs that ordinarily are not considered to be affected in this disease.

The exact site of deposition of the amyloid could be determined in some locations. By use of the Gomori reticulum stain followed by methyl violet the material could be seen closely applied to the reticulum fibers between the sinusoids and the cords of hepatic cells. The same site of deposition was noted in the adrenal gland. In the heart, the amyloid was located on the reticulum between the muscle fibers and the adjacent capillaries. In situations where the small blood vessels of an organ were the site of infiltration, the substance was seen in the media where it encased the individual smooth muscle cells. In some locations, notably the kidneys and the mucosa of the gastrointestinal tract, the amyloid was laid down in the walls of the capillaries, the endothelial cells of which were alone visible within the thickened walls. In the thyroid and pancreas the material appeared to be in the connective tissue. The adipose connective tissue near the adrenals in a few of the cases showed the amyloid to be deposited on the surface of fat cells, giving their walls a thickened appearance.

The only really important clinical signs and symptoms of amyloidosis in this group of cases were those due to involvement of the kidneys. In only one case was hepatomegaly definitely due to infiltration of the liver with amyloid. In an additional case there were minimal signs of hepatic failure, apparently the result of amyloidosis. The rarity of signs of hepatic failure in this disease has been stressed by Tiber, Pearlman and Cohen [18] and by Spain and Riley.[19] As emphasized by Kruger and Gerber,[20] however, hepatomegaly and decreased hepatic function are not uncommon in secondary amyloidosis. Adrenal cortical insufficiency was not observed in this group. Snapper and Ch'in [21] and Mendel and Saibil [22] are among those who have observed Addison's disease in amyloidosis. Stemmerman and Auerbach [16] found indisputable evidence of Addison's disease in none of 354 examples of adrenal amyloidosis. It was noted in early times [8] that diarrhea may result from enteric amyloidosis, but only one of the patients in the present series had diarrhea associated with amyloid in the gastrointestinal tract.

In all the cases of this series typical staining reactions were displayed. The amyloid stained metachromatically with methyl violet and crystal violet.

It became yellow when stained by the van Gieson method. It stained red with Congo red and pink with hematoxylin and eosin. The van Gieson stain was found to be useful in differentiating amyloid from collagenous connective tissue or hyalin. These latter tissues, when present in a density similar to that of amyloid, stain red. This staining characteristic is of considerable value in cases in which there are atypical reactions to other stains.

Summary

Thirty examples of secondary amyloidosis were studied with special attention to distribution of the amyloid and to important symptoms resulting from it. A well-marked nephrotic syndrome occurred in four cases. Severe renal insufficiency developed terminally in three cases. The amyloid was deposited chiefly on the connective tissue or in the blood vessel walls of affected organs. This substance stained typically with methyl violet, Congo red and van Gieson stains.

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ON THE SIGNIFICANCE OF THE NORMAL ELECTROCARDIOGRAM IN OLD AGE*

By THEODORE T. FOX, M.D., *New York, N. Y.*

IN 1939 a group of 300 ambulatory inmates of the Home and Hospital of the Daughters of Israel, an institution for the care of the aged, was subjected to a cardiovascular study, and the results, stressing particularly the electrocardiographic changes in senescence, were reported in the literature.[1] Of the 300 inmates 200 had abnormal electrocardiograms and 100 cases had normal tracings. A normal tracing was considered *normal* by the usual standards: no allowances were made for certain deviations "frequently" (?) observed in older people. It was concluded that the incidence of abnormal electrocardiograms increases with age and is fairly parallel to the occurrence of heart enlargement; and although the abnormal tracing is compatible with normal clinical behavior because of the lessened physical load in senescence, it is, however, an indication of disease, and is of prognostic significance. Seven years later the clinical course of the 100 inmates with normal tracings was reviewed. The evolution of the normal electrocardiograms was studied in order to ascertain whether it carries with it a reflection of clinical events and prognostic significance.

RESULTS

Forty-seven of the 100 inmates with normal electrocardiographic tracings in 1939 were found to have abnormal electrocardiograms at the end of seven years. Twenty-two of this abnormal group were living and 25 were listed among the dead. The electrocardiographic abnormalities in the 22 living inmates were as follows: RST changes (depression) in five cases, T-wave inversion in eight cases, simultaneous RST changes and T inversion in six cases, intraventricular conduction impairment in one case, abnormally deep $Q_{2 \text{ and } 3}$ in one case, and low voltage in standard leads in one case. The abnormalities in the tracings of the 25 who died within the seven years were as follows: RST changes in nine cases, T-wave inversion in nine cases, simultaneous RST and T changes in five cases; auricular fibrillation was noted in three cases, auricular flutter in one case, first stage A–V block in two cases, bundle branch block in one case, low voltage of the standard leads in one case, nodal rhythm in one case. In three cases the abnormalities were combined, i.e., bundle branch block and auricular fibrillation. The hundred inmates studied can be divided in relation to the type of electrocardiographic tracing into four groups: living with normal tracings, living with abnormal tracings, dead with normal tracings, dead with abnormal tracings.

Group I. Living with Normal Tracings (table 1). There were 37 in-

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From the medical service of the Home and Hospital of the Daughters of Israel, New York, N. Y.

mates in this group, 17 males and 20 females. The majority were between 70 and 79 years old. Only 13 cases in this group presented heart enlargement on fluoroscopic examination, 24 had hearts of normal size. There were only four cases with an elevated diastolic blood pressure reading (above 90). The intercurrent illnesses listed on the charts of these inmates in the course of seven years included the following conditions and diseases: prostatism, herniotomy, fracture, pneumonia, cystitis, enteritis, bronchitis, glaucoma, phlebitis, pyelitis, diabetes, bronchiectasis, cholecystitis. Chest pain was mentioned to have existed on occasions in two cases, congestive failure in one case, failure was questioned in two cases.

TABLE I *

	Male	Female	Both Sexes	Age 60 Plus	Age 70 Plus	Age 80 Plus	Age 90 Plus	Enlarged Heart	Heart not Enlarged	Systolic Hypertension	Diastolic Hypertension	Normal Tension
I. Living with normal tracing	17	20	37	3	29	5	0	13	24	26	4	7
II. Living with abnormal tracing	12	10	22	0	14	7	1	8	14	13	4	5
III. Dead with normal tracing	8	8	16	2	8	6	0	8	8	9	2	5
IV. Dead with abnormal tracing	8	17	25	6	10	9	0	17	8	11	7	7

* The ages indicated in this table are as of 1939, and so are the results of fluoroscopic examination of the heart. The blood pressure classification is based on the average of readings recorded in the course of the seven years observation.

Group II. Living with Abnormal Tracings (table 1). There were 22 cases in this group, 12 males and 10 females. The majority were between 70 and 79 years old. About one third in this group had fluoroscopic evidence of heart enlargement. Only four had a diastolic tension over 90 mm. of mercury. The duration of the existence of the electrocardiographic abnormalities in this group was as follows: in eight cases (37 per cent) it was five years; in 10 cases (46 per cent) it was three years; in one case, four years; in two cases, two years; in one case, one year. In other words, in eight cases it took two years for the abnormality to appear in the electrocardiogram, in 10 cases four years, in two cases, five years, in one case three years, in one case six years. The intercurrent illnesses listed in this group are as follows: epilepsy, pneumonia, Parkinson's syndrome, phlebitis, diabetes, polycythemia (with cerebral thrombosis), prostatism, gall-bladder disease, bronchitis, enteritis, cystitis, asthma (cardiac?). There was one case of coronary closure. Three cases had episodes of congestive failure. Of the eight cases who were alive five years after the abnormal tracings were recorded, only three had enlarged hearts and only one case belongs to the group of diastolic hypertension.

Group III. Dead with Normal Electrocardiograms (table 1). There were 16 cases in this group: eight males and eight females. The majority

were between 70 and 79 years old. Fifty per cent of this group had fluoroscopic evidences of heart enlargement. Only two inmates had an elevated diastolic tension. The intercurrent illnesses in this group were as follows: pneumonia, gall-bladder disease, colitis, bronchitis, upper respiratory infections, pyelitis, cystitis, diabetes, fracture, phlebitis, paresis, anginal syndrome. Coronary closure figured as a cause of death in three cases and was a possible cause of death in one case. The duration of life of the inmates in this group from the beginning of the observation period (1939) was as follows: two years in five cases, four years in six cases, five years in two cases, six years in three cases.

Group IV. Dead with Abnormal Electrocardiograms (table 1). There were 25 cases in this group: eight males and 17 females. Ten belonged to the eighth decade and nine to the ninth decade. Seventeen cases had enlarged hearts on fluoroscopic examination, eight had hearts of normal size. Seven cases had an abnormally elevated diastolic tension. Intercurrent illnesses for which the inmates required hospitalization in the course of seven years of observation included congestive failure (in five cases), cerebral thrombosis, pyelitis, colitis, pneumonia, fracture, diabetes, cholecystitis. The cause of death was listed as coronary occlusion in six cases, failure of circulation in two cases. The cause of death in the rest of the cases was not directly connected with the circulatory apparatus. The duration of life of the inmates in this group from the beginning of the observation period (1939) was as follows: almost seven years in four cases; six years in two cases; five years in seven cases; four years in four cases; three years in three cases; two years in five cases.

The duration of life from the time the abnormal electrocardiogram was detected was as follows: a few days in two cases, one month in one case, two months in one case, three months in one case, five months in one case, eight months in one case, 12 months in five cases, 15 months in one case, 18 months in one case, two years in four cases, three years in four cases, four years in three cases, five years in one case. Twelve cases lived one year or less from the time the abnormal electrocardiogram was recorded. Of these six had enlarged hearts and only one was in the group with diastolic hypertension. In 12 cases two years elapsed from the beginning of the observation period (1939) before electrocardiographic abnormalities appeared; in four cases, four years; in four cases, three years; in two cases, 21 months; in one case, 18 months; in one case, six and one-half months; in one case two and one-half months. In the five cases in which the electrocardiographic abnormalities appeared in less than two years from the beginning of the observation period (1939) all had enlarged hearts.

Comment

Obviously the series of cases analyzed is too small to permit definite conclusions. However, information on certain points is furnished by this study. First, as to the type of electrocardiographic changes that are apt to develop

after the onset of senescence: Most papers on this subject describe the electrocardiographic changes as observed at a given moment without reference to the time of development of these changes. Thus, in a previous study of the same block of senescent population,[1] the incidence of auricular fibrillation was given as 4 per cent; prolonged A–V conduction, 13.3 per cent; prolonged I–V conduction, 13 per cent. Apparently the conduction difficulties occur mostly earlier in life. In the present study, comprising a period of seven years, auricular fibrillation was still observed in 3 per cent of the cases, but A–V and I–V block were observed only in 2 per cent of the cases. Most of the changes that are apt to develop in this age group are apparently in the RST segment and T-wave configuration. The development of the abnormal electrocardiogram was not connected in the majority of cases with clinical evidence of heart disease. On the other hand, the five cases in group I who exhibited cardiovascular embarrassment did not show abnormal electrocardiograms.

Does the development of an abnormal electrocardiogram in senescence signify a poor prognosis? Reference to table 1 reveals the fact that there were more inmates alive with a normal tracing than with abnormal ones (37 against 22), and there were more dead cases with abnormal tracings than with normal ones. On the other hand, the difference between the living with abnormal tracings and the dead with abnormal tracings is not great. The duration of life from the time the abnormal tracing was recorded in the cases of group IV was short in the majority of cases; on the other hand in group III, 37 per cent of the cases were alive at least five years from the time the abnormality in the tracing was detected. Apparently, then, there must be other factors in determining the prognosis of the aged person. Age does not seem to be the factor. The average age of those alive (group II) with an abnormal electrocardiogram five years or longer was 84 (in 1939). In group IV only one inmate with an abnormal tracing lived five years. He was 92 years old when he died. Fifteen cases lived two years or less. The one inmate with an abnormal tracing who lived only two months was 86 years old at the time of death.

The important factors associated with the electrocardiographic changes seem to be the state of the blood pressure and the heart size. It is to be noted that in group II most cases had a systolic hypertension, but of greater significance is probably the fact that most cases in this group did not have enlarged hearts.

Group IV had relatively more cases with diastolic hypertension than the other groups, but the outstanding feature in this group is the number of cases with heart enlargement (more than two thirds). It may be of significance also that the electrocardiographic changes in this group included five cases of arrhythmia and two with A–V block.

The importance of heart enlargement as a prognostic factor in senescence is also seen in the analysis of group III. Fifty per cent in this group had enlarged hearts.

Summary and Conclusions

One hundred inmates of an institution for the aged showing normal electrocardiograms were followed for a period of seven years. By the end of the second year, 22 cases were found to have abnormal electrocardiographic tracings. By the end of the fourth year, 36 cases possessed abnormalities in the electrocardiograms. By the end of seven years 47 inmates had abnormal changes in the electrocardiogram. In evaluating the significance of the abnormal tracing the related factors considered were age, the level of blood pressure and the presence of heart enlargement. It became apparent that while the occurrence of the abnormal electrocardiogram in senescence has a prognostic significance, it is the presence of heart enlargement that is a more determining factor of the life span of the aged individual.

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NEWER CONCEPTS OF MEDICAL CARE*

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Physicians are confronted with the possibility of drastic changes in methods of medical practice if Congress enacts certain legislation that to some is a measure for health insurance and to others represents an attempt to socialize medicine. Such legislation has been proposed because a sizable segment of the population of this country cannot enjoy the full benefits of medical care of the high caliber available today in only the relatively few teaching centers. The reasons usually given for the maldistribution of medical care are those related to social and economic factors. The cures proposed are likewise chiefly social and economic. There is still another aspect of this problem, however, that has not been given as much consideration as its importance seems to warrant, namely, the relationship between medical care and medical education. It is the purpose of this discussion to point out practical methods through which medical care can be improved in a wide area, chiefly through the medium of postgraduate medical education.

There are many intangibles that influence medical care. One of these is concerned with the supposedly well-established fact that everyone should have a family physician as his counselor on all medical matters; yet many have no family doctor, not necessarily because none is available, but because some rely on cultists for much of their medical care and others are always "shopping around" from one doctor to another, or visiting specialists or clinics without being referred. Because of their lack of proper guidance, they are apt to get poor medical care and at the same time pay heavily for it.

Why have some people lost faith in the medical profession to the extent that they risk their lives by placing themselves in the unqualified hands of the cultists? Why have others lost faith in the family physician to the extent that they "shop around" for their medical care? Undoubtedly, in a few instances this loss of faith has developed because of the occurrence of some real or imagined blunder in diagnosis or management, but these account for only a small minority. It is probable that the great majority of patients in this group are suffering from a variety of psychologic or frankly psychiatric disorders. Patients in this category are frequently poorly handled by physicians—general practitioner and specialist alike. They are often misdiagnosed and treated for illnesses they do not have; or if the disorder is recognized, they rarely receive the painstaking and time-consuming attention they require. Not finding the relief they seek from the one they had considered the family physician, they naturally look for help elsewhere. In order to prevent further derelictions in this direction, all physicians should

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be trained in modern methods of recognition and management of the mild psychiatric disorders. The training of thousands of psychiatrists may not necessarily be the answer, for there is as yet no proof that in such a tremendous task psychiatrists would produce better results than sympathetic family physicians. This is a job for postgraduate education at the general practitioner level.

Another of the intangibles influencing medical care has to do with the tendency of young physicians to settle in urban areas and to avoid rural practice. Closely allied is the rapidly increasing trend toward specialization and away from general practice. These factors have given rise to a very poor distribution of medically trained personnel.

Why do physicians tend to settle in medical centers and avoid rural areas? The reasons usually given are the availability of greater economic opportunities and a more diversified group of social outlets in urban centers than are apparent in rural communities. The ambitions of physicians' wives are supposed to be important factors. Although it is difficult to appraise the last item, the economic and social factors are certainly not so paramount as might be presumed. While it must be admitted that the maximum income that may be achieved by an unusually successful practitioner in the city is probably greater than the top level that may be reached in the country, this maximum is reached by relatively few individuals. For every physician in the high income brackets in urban practice, there are dozens that after many years of struggling and disappointment attain only modest success. In rural areas where the demand for medical care is greater, a young physician can realize a good standard of living quickly. If he is unusually gifted, a substantial financial reward is assured. On a comparison of living costs in the country with those in the city, the average rural practitioner is very apt to be far better off than his urban counterpart. Also, social outlets are readily available to the country doctor and his wife. They automatically become leaders in their community and a host of activities are theirs for the asking. With modern transportation, they are rarely more than a few hours' distance from a city and its mundane pleasures.

If social and economic opportunities are not the important attractions, what *are* the factors that make young doctors choose an uncertain medical existence in the city? It is becoming apparent that physicians believe that only in the vicinity of a well-equipped and well-staffed hospital is it possible to practice the type of medicine they have learned. They feel that only in this manner will they be able to bring the best medical care to their patients. More often than not they will settle near the hospital where they received at least a part of their training. All physicians know that the best medical care is centered about teaching hospitals. They are anxious to be connected with the staff of such hospitals not only for the prestige that the association carries, but also for the opportunities offered for continuing medical education. They are willing to make financial sacrifices and spend many unpaid hours in outpatient service in exchange for the assurance that they will be

able to keep abreast of advances in medical science through staff meetings and other educational activities peculiar to teaching hospitals. This intellectual stimulation is more valuable to them than economic and social prestige.

Why has the trend toward specialization become so pronounced? Among recent graduates the idea of becoming a specialist seems to be almost an obsession, partly because of the preference given to specialists in the military services and in Veterans Hospitals. The nature of these services is naturally taken as a pattern that will be followed should socialization of medical practice become a reality. Also, the financial subsidy given to veterans under the "G. I." training program has made this type of training possible for many who would otherwise have been unable to afford the sacrifice of extra nonproductive years. The trend toward specialization was, however, well-established before the war and even before the threat of socialization made its appearance. It is true, statistics show that men with specialties earn higher incomes than nonspecialists; but these are the most ambitious group of doctors, and who is to say that they would not have been equally successful had they chosen general practice? A young man must have had a touch of altruism to have chosen a medical career in the first place. Economic aspects, therefore, may not necessarily be the only ones involved in making decisions as to the type of practice preferred. Other factors may also be involved, and these may be related to some phases of medical education just as those already discussed.

The strong trend toward specialization has been influenced by resident-training programs designed to meet requirements of American Specialty Boards. The almost universal tendency in making resident appointments is to select doctors directly from their internships or assistant residencies. Once a physician enters practice, the chain of opportunity for advanced training is broken and it becomes extremely difficult for him to gain the knowledge and training necessary to qualify him as a specialist. The decision of whether or not to specialize must be made very shortly after graduation from medical school; once the decision to enter the general practice has been made, it is nearly irrevocable. Rather than make this decision, nearly all who can are electing to take advanced training. If general practitioners who for one reason or another decide to try to obtain additional training in order to qualify as specialists could easily get that training (provided, of course, that they have the necessary intellectual, moral, and educational backgrounds), the whole trend toward early specialization might be reversed. More and more young doctors might decide to do general practice for several years to gain financial independence and experience, and then, knowing exactly what they want, would return to teaching hospitals for several years to learn a new field of medicine thoroughly. Perhaps, by having more mature residents, the training program could be revised and shortened. As it is now, men and women are being turned out as specialists at an early age when neither patients nor more mature doctors have complete confidence in their judgment.

Medical practice has become so complex that it is impossible for one man to become proficient in all of its many aspects. The general practitioner is constantly confronted with problems he feels unqualified to solve. His undiagnosed patients eventually may reach a specialist or a clinic, with or without being referred. In either case, at present there is probably not more than a 50 per cent chance that the patient will return to him for further care. The general practitioner therefore loses many of his most interesting and stimulating cases. He resents this but feels it must be an inevitable result of his lack of knowledge. The specialist, on the other hand, sees a selected group of cases representing only that narrow segment of the entirety of medical practice in which he is most proficient. Through his special training and continuous experience, he is able to give authoritative opinions in nearly all cases. Thus he avoids the intellectual frustrations of the general practitioner and in addition is stimulated by constantly seeing unusual cases. In the group clinic, the same factors operate. When confronted by a diagnostic problem, the clinic staff member is protected from intellectual frustration because he has recourse to laboratories that may aid him or he can pass the patient along to a colleague who presumably knows more about the particular group of diseases than he. Also, the clinic promotes constant exchange of ideas between the various departments and opportunities for postgraduate study without the risk of losing a practice. Thus, one of the important appeals of practice in a specialty or in a clinic is related to the stimulus of continuing education; and the lack of attraction to general practice is related, at least in part, to the absence of this stimulus.

Although specialization and group practice are obvious solutions to some of the problems raised by the maldistribution of medical care, they may create problems equally serious. Under present conditions many specialists and group clinics are in open competition with general practitioners. This is highly uneconomic. Most informed persons are in agreement that a well-trained general practitioner is capable of adequately managing a large percentage of all illnesses. Most of the infectious diseases are self-limited; with modern therapeutic methods, the general practitioner can achieve excellent results with this group. He is perfectly capable of minor office surgery, too. Another sizable group of patients can similarly be managed satisfactorily by the general practitioner once the correct diagnosis has been established. These patients are those with cardiovascular diseases, many hematologic disorders, endocrinopathies, metabolic disorders, rheumatic diseases, allergies, and some neurologic disorders. (Methods of obtaining necessary diagnostic aid will be discussed later on.) Most of the psychoneuroses can probably be best treated by an understanding family physician who gains knowledge of family social and economic problems through close contact. In the group of patients with incurable diseases, the general practitioner can often do just as much as the specialist in giving comfort. There remains only a small group of patients requiring specialized medical or surgical knowledge and care.

Group clinics and specialists have a certain aura that attracts patients. If they accept and treat nonreferred cases, as most of them do, the patient in most instances pays more for his medical care than the nature of his disease warrants, and the general practitioner suffers accordingly. This sort of practice is also uneconomic in that the man with special training becomes bogged down with routine problems not requiring the exercise of his special talents. In the clinic the patient is apt to lose his identity, being shifted from one specialist to another without having any one physician his counselor. Finally, few clinics are prepared to care for patients in the home. Thus, when acute illness occurs, a strange physician is called or the patient is hospitalized in the clinic, perhaps unnecessarily.

Another element that many consider one of the primary causes of the poor distribution of medical care is the supposed great lack of hospital facilities nearly everywhere. Most communities and hospitals have blueprint plans for the expansion of existing hospital activities or the construction of entirely new units. It would seem that before ambitious building is undertaken, studies should be made of existing hospital facilities. Are they being efficiently utilized? Are all hospital admissions justified? There is a reasonable suspicion that they are not. Many surgical operations are performed unnecessarily. Many patients are admitted to hospitals for diagnostic study, when with proper accommodations they could just as easily, and at less expense, be examined as ambulatory patients. Also, it is not enough to build hospitals and to equip them with elaborate machines, nor even to make it possible for every patient to afford a hospital experience. It is not the physical equipment, nor the amount of money spent, nor the number of tests performed that determines the quality of medical care in a hospital; rather, it is the skill with which diagnoses are made and treatment administered. This type of proficiency requires a high degree of technical knowledge—seasoned by experience—and is found only in well-trained, up-to-date physicians. (Some of the most grievous errors occurring in medical practice result when physicians attempt diagnostic and therapeutic procedures for which they are not qualified by their training.) The problem, then, is that of placing competent men in key positions and then making certain that they keep abreast of medical progress. These, again, are questions closely related to medical education.

At the same time that an increase in the number of hospital beds is being proposed, the unprecedented demand for interns remains unsupplied and still there are no advanced plans for increasing the number of medical graduates. How will new hospitals improve medical care if they cannot be properly staffed? This question becomes even more pertinent when it can be pointed out that a majority of our present hospitals do not now meet the minimum acceptable standards as training centers for interns and only a relatively few are approved for the training of residents. Yet interns and residents are almost a necessity for the giving of first-class medical care. Teaching hospitals, on the other hand, are swamped with applications. In order to try

to meet the unprecedented demand for special training, many of them are accepting more interns and residents than they need.

Hospitals desiring approval as training centers must have an active clinicopathologic laboratory under the supervision of a competent pathologist, a good department of roentgenology headed by a well-trained radiologist, and a department of anesthesia under competent direction. Teachers in their clinical departments must be men of approved standing. In many instances, the establishment of these services is opposed by physicians already practicing in areas dependent upon nonapproved hospitals. Artificial barriers are imposed by monopolistic control of hospital policies, the seniority system, and arbitrary staff appointments. Undoubtedly, since there are many competitive situations in medical practice, these barriers serve as economic bulwarks to protect the earnings of physicians already established. In addition, however, they may be based on matters relating to medical education. Physicians whose medical knowledge has failed to keep up with modern developments cannot stand competition on an equal footing with those that are equipped with many of the latest refinements of diagnosis and treatment. Many practice on a level not far removed from that attained at graduation from medical school. Under present conditions, the lack of advanced knowledge on the part of some older physicians is due largely to the lack of opportunities for gaining this knowledge without considerable sacrifice. The use of protective barriers is therefore found necessary to preserve prestige. Were the opportunities readily available and their medical knowledge kept constantly up to date, they would not need counterfeit devices but would have the natural advantages of skill gained through experience plus the confidence of their patients. A much healthier form of competition would thus become evident. It is important that these men become aware of the tremendously important part teaching hospitals can play in advancing the medical thinking of their staff members by virtue of their teaching activities and the stimulating influence of contact with residents who have received part of their training in other medical centers. What is necessary is help from some agency in the establishment and maintenance of acceptable educational programs in all hospitals.

It is apparent, then, that the problems of continuing medical education of practicing physicians are interrelated with improvement of the standards of medical care. Medical education of all types obviously should be a function of medical schools; yet until recently, the idea of continuing the education of practitioners has with few exceptions been neglected by them. The schools have felt that their functions were completed with the granting of the M.D. degree or on completion of the university hospital training or with the giving of a few postgraduate courses. Many schools are now belatedly realizing that it is their responsibility to aid in the continuing education of physicians throughout their active professional careers.

The following is an outline of the activities of one medical school that has been actively interested in this problem for more than 17 years. Its

program is now serving as a model for many other medical schools and health agencies in this country and abroad.

In 1931, Dr. Joseph H. Pratt,[1] Dr. John George Gehring and Dr. George Bourne Farnsworth, at the instigation of and with the philanthropic aid of Mr. William Bingham II, initiated a unique program designed to improve the quality of the medical care of a rural community (Rumford, Maine) by increasing the educational opportunities of practicing physicians. Through the efforts of these men and Dr. Samuel Proger,[2] the present director of the program, the original idea has been considerably developed and expanded so that its benefits are now readily apparent throughout most of the state of Maine, parts of Massachusetts, and to a lesser degree in all of New England.

In the Bingham Associates Program, the principles previously outlined are given primary consideration. Every effort is made to protect the dignity of the general practitioner. He is encouraged to become an integral part of the program—all factors tending to submerge his importance being carefully avoided. By making the general practice of medicine an attractive vocation and by offering ever-increasing opportunities for continuing medical education, many young physicians are beginning to set up practice in the areas of interest. Hospital facilities in regional areas are being strengthened by making it possible for them to have the services of trained personnel to aid in routine studies and to have ready access to expert opinions in various fields whenever necessary. Existing hospitals are used, the emphasis being upon improving personnel and function rather than structure. Competitive aspects are strictly avoided by having the family physician retain control of his patients at all times. Regional hospitals are being developed as teaching centers with the consequent attraction of more young physicians to remote areas bringing with them many coincident benefits in medical care.

At its inception it was realized that as an educational endeavor this program had to be affiliated with a medical school and that there must be a medical base for the direction and coördination of its many activities. The New England Medical Center now serves as that base. This unit comprises the Tufts College Medical School, the New England Center Hospital (the Joseph H. Pratt Diagnostic Hospital, Farnsworth Surgical Building, and Ziskind Research Laboratories), the Boston Dispensary and the Boston Floating Hospital. While there aré many interlocking functions between the various undergraduate departments and the Postgraduate Division of the Medical School, many members of the faculty have their primary interest in the field of continuing medical education. Each division is strengthened by virtue of this association. Undergraduates benefit from contact with men who have an understanding of the problems of general practitioners; the postgraduate program benefits through its affiliation with the medical school, particularly in the basic science departments.

The postgraduate or continuing education of a physician is carried on in various ways. One of the most popular methods today is by means of

refresher courses varying from a few days to several months in length. The advantages of this type of training are that courses are usually given in a medical center by a group of qualified teachers and a great mass of material can be presented within a short period. Some physicians feel that attendance at such courses at regular intervals keeps them up to date with advances in medical thinking. The large enrollment in most postgraduate seminars, and at state and national medical society meetings is proof of their popularity. At the same time it must be admitted that there are definite limitations to this method of postgraduate training. Experience has shown that only about 15 per cent of practicing physicians avail themselves of postgraduate training programs. Some never attend. At best, refresher courses serve only as a temporary stimulus and their benefits are short-lived unless implemented by other experiences. At Tufts, many short postgraduate refresher courses are given throughout the year but these are considered only as interval educational experiences that need many other influences to direct and expand them. A nine-month graduate course in Internal Medicine is offered, with precedence in the selection of candidates being given to acceptable physicians who have been in general practice.

A much more fruitful field for continuing the education of the practicing physician is the hospital where he treats his sickest patients. No medium is more valuable for teaching than bedside instruction. New methods of diagnosis and treatment demonstrated on his own patients immediately become the personal knowledge of the physician. Thus arose the concept of aiding local hospitals far removed from medical centers to become in themselves educational institutions.

The basis of a teaching program in a hospital is the existence of good diagnostic facilities. As a minimum these imply adequate clinicopathologic and roentgen-ray departments each under competent supervision. The pathologist's findings on examination of surgical and autopsy specimens serve as a constant check on the accuracy of clinical diagnoses. His clinical laboratory is necessary for diagnostic studies and the proper control of many therapeutic procedures. He is apt to be one to introduce many new technics that aid in improving medical care. Likewise, medical care is greatly enhanced when the services of a first-class radiologist are readily available.

With the aid of financial grants from the Bingham Associates Fund and the Rockefeller Foundation, it has been possible to establish new roentgen-ray and laboratory departments in hospitals where these services had been lacking and to expand existing facilities in others so that their benefits could be extended to remote areas. This was done through the development of a hospital extension program. Direct affiliations were established between the medical center base in Boston and regional hospitals in key centers in the areas served. The regional hospitals in turn became affiliated with the several small community hospitals within their zone of influence. The groups of small hospitals thus work together on problems of mutual interest and through the regional hospital have direct channels to the medical center.

Animosities that might arise if it seemed that the medical center was assuming authority in matters affecting physicians in remote areas are thus avoided.

In Maine, the Eastern Maine General Hospital in Bangor serves as the regional center in the northeastern area and is affiliated with 14 community hospitals within a radius of about 200 miles, and the Central Maine General Hospital in Lewiston serves as the regional center for 13 other hospitals within a radius of about 70 miles in the interior. In Massachusetts, where the program has been in operation only about three years, the possibilities and difficulties of another type of arrangement are being explored. Four hospitals of moderate size in adjacent towns all seemed to have common problems; so this group has been organized as a single unit on a coöperative basis. They now share equally the services of a pathologist, residents and other mutual benefits. Three smaller community hospitals have become affiliated with this group. Other hospitals in Massachusetts have not as yet been organized into coöperating groups, but several in scattered areas are affiliated directly with the medical centers for various parts of the program. One of these is located in a sizable central city (St. Vincent Hospital, Worcester) and another is in a large suburban community (Lynn Hospital, Lynn). Each hospital or group of hospitals presents problems that differ from those of others. No single pattern can be applied to all; thus the program must be kept flexible so as to meet circumstances that vary not only from place to place, but also from time to time in the same community. The medical center and the regional hospitals must be sensitive enough to adapt readily to these changes.

The clinicopathologic departments in the regional hospitals are so organized as to be able to serve the affiliated community hospitals, none of which would demand the services of a full-time pathologist. All surgical specimens are examined in the main laboratory and prompt reports go to the surgeon, perhaps many miles distant. In doubtful cases the specimen is forwarded to the pathologic department at the medical base in Boston for further opinion. The radiologist in the regional hospital interprets all films taken by technicians in the community hospitals and in some instances makes regular visits for fluoroscopic studies. In other areas two small hospitals are served directly by a qualified radiologist. An example of the type of improved service in pathology resulting from this arrangement is found in the statistics from the western Massachusetts group of hospitals. Prior to the institution of this program very few autopsies were performed in this area. In the first year after a pathologic service was organized, nearly 200 postmortem examinations were carried out.

It is not planned that the financial subsidy for the development of these services shall continue indefinitely. The initial cost is the chief obstacle. As services become well established, each hospital gradually assumes its proportionate share of the costs since the charges for services rendered can then very legitimately be passed on to the patients who receive the ultimate

benefits in improved medical care. After an interval of several years, this part of the program becomes self-supporting.

In order to enable the pathologists and radiologists of the regional hospitals to enjoy the stimulating influences of an academic atmosphere, close liaison is maintained between them and their respective departments in the medical center. Some of these men in the peripheral hospitals hold academic ranks in the medical school. They are all encouraged to conduct weekly seminars for the house staff and for local physicians. Many educational opportunities for general practitioners present themselves in these conferences. Other important phases of this academic connection are the biweekly pathologic and roentgen-ray seminars held in Boston. The regional pathologists and radiologists from the various areas bring their problems to these meetings for discussion by other experts in their respective fields.

In the conferences opinions are readily available to aid in the solution of difficult diagnostic problems that may have arisen in a remote hamlet. The economy of this plan is at once apparent, the special talents of the experts being utilized only in problem cases, but being readily available to any patient should necessity demand.

Hospital extension services have been carried into several other fields. In electrocardiography, the objective has been to urge that tracings be made in the smaller community hospitals under conditions comparing favorably with those in the metropolitan center. A local physician is encouraged to learn to interpret electrocardiograms accurately. Elementary and advanced courses in electrocardiography are given for this purpose from time to time at the medical center. The physician sends a duplicate of each tracing to the regional center for a check on his opinion by a competent cardiologist. In unusual cases, the opinions of several cardiologists at the medical center are readily available. The local physician thus develops a new sphere of medical interest and is constantly expanding his knowledge while a valuable medical service is being added to his hospital.

The auxiliary services of a hospital need the constant stimulation offered by educational experiences just as the clinical departments. These include the laboratory and roentgen-ray technicians, dietitians, librarians, nurses and even hospital administrators. Scholarships are granted to technicians for advanced and special studies. Technicians in each small hospital annually spend one month in Boston for the purpose of improving technics and learning new procedures. An itinerant technician is provided to substitute in the affiliated hospital for the duration of the course. An attempt is made to standardize laboratory procedures by having the central laboratories send stock solutions of various reagents to many of the hospitals. By means of this arrangement the number of variable factors is reduced and accurate results are more easily obtained in small laboratories.

Postgraduate study for dietitians in community hospitals is made possible largely through scholarships enabling them to spend one month each

year at the New England Medical Center where they are given a continued course of instruction and kept informed of progress in their field.

The Gerrish Library at the Central Maine General Hospital in Lewiston serves as a central library for the entire Lewiston group. The librarian prepares bibliographies, sends books to practitioners, and maintains a traveling mail service on current journals. The Bangor and western Massachusetts groups of hospitals have been given memberships in the Boston Medical Library to supplement their own library facilities.

Consultation between hospital administrators at various levels is encouraged. Advice in hospital organization methods from a disinterested but well-qualified outsider often helps to overcome serious internal difficulties.

One of the most effective ways to stimulate advances in methods of medical practice in communities far removed from a medical center is through residents and assistant residents who have just completed a period of training in a medical center. These men come to the peripheral hospital disciplined in the most recent refinements in diagnosis and treatment and can impart their knowledge to local physicians at the point where it is apt to be most effective—at the bedside of a patient. In order to attract men of high caliber as teaching residents, hospitals must be approved as training centers and other inducements must be offered as well. The basic services in the regional hospitals have been strengthened so that approval for resident training will be assured. In the Bingham Associates Program a comprehensive plan has been devised for the rotation of residents from the peripheral hospitals through the medical center and back to the regional areas as teaching fellows. In their year as teaching residents, they are adequately paid and are given faculty appointments as instructors in the medical school. They have the responsibility of furthering the better organization of the medical services by supervising the teaching of medicine to assistant residents and interns and stimulating clinical staff meetings and journal clubs. They visit the medical center at regular intervals to attend conferences and thereby add continuously to their fund of medical knowledge. Similarly, residencies have been established in some of the regional hospitals in pathology and radiology. The value of this program in improving the standards of medical care in the peripheral hospitals cannot be challenged. In addition, many competent young men have been attracted to areas that otherwise they would never have considered as places to live and practice.

A further important phase of the hospital extension program is that of teaching ward rounds. These are designed to give the house staff of the regional hospitals regular instruction by experienced teachers as well as offering free consultation services in difficult cases. The visiting hospital staff is, of course, welcome to attend. Bimonthly sessions are held and guest instructors are invited from Boston or other medical centers. These sessions have proved to be popular not only with the men in the regional centers but also with the instructors who have found a great wealth of unusual clinical material at points remote from the medical center. Often, it

is possible for the instructor to make suggestions regarding the adoption of procedures that would facilitate the diagnosis and treatment of other patients in the regional hospitals. Local physicians and house officers are stimulated to improve the quality of their case work-ups. Certainly, patients benefit through generally improved standards of medical care.

It has been pointed out that the well-trained general practitioner is capable of adequately caring for all but a small percentage of the medical problems he meets provided that clinical diagnostic aid is readily available. In the Bingham Associates Program the Joseph H. Pratt Diagnostic Hospital was organized for this purpose. Here are centered the technical facilities and trained personnel necessary for diagnostic study of all types. The full-time staff is not large, but in special cases consultants expert in all fields can be called upon from the great wealth of such men in Boston.

There are several rather unique features about the Pratt Hospital. A patient is accepted for study only if he has been referred by a physician who continues to retain complete control of his patient. No treatment is given at the hospital unless this is the wish of the referring doctor, and if surgery is indicated, arrangements are made only after consulting him. In nearly all cases, when studies have been completed the patient is returned directly to the care of his own doctor. The hospital staff gives the patient little information other than reassurance regarding negative findings in order to avoid any tendency to discredit previously made diagnoses. In this manner, the dignity of the family physician is preserved. He is encouraged to seek consultation in puzzling cases early rather than to treat the patient aimlessly and hope for improvement, and the patient consequently is benefited by improved medical care.

No problems have been encountered in using patients of the "private" class for teaching purposes. Fourth-year medical students serve as clinical clerks, their work being supervised by residents and senior staff members. The most interesting patients are presented in daily staff conferences attended by many undergraduate and postgraduate students. Often, at these conferences, opinions are obtained that are of considerable value in the diagnosis and management of these patients.

At the present time when income from endowments is contracting, medical schools are finding it increasingly difficult to pay salaries to clinical teachers commensurate with their earning capacity in other types of practice. Standards of teaching under these circumstances are apt to deteriorate. The large number of paying patients examined at the Pratt Hospital permits the payment of adequate salaries to its full-time staff members, all of whom are actively engaged in clinical work, teaching, and research. In time, one of the chief sources of income for medical schools may be from fees paid by patients for specialized services in the teaching hospitals. It is important, however, that the teaching hospitals adopting such a program retain their autonomy or else they may be forced into mass production methods in order to meet the almost endless financial needs of the nonclinical branches of the

medical school. By remaining independent of these pressures, proper balance can be maintained between clinical, teaching, and research activities.

Each patient seen at the Pratt Hospital is considered to be an ideal medium for conveying information of educational value to the referring physician to whom a complete transcript of the hospital record is forwarded on the completion of studies. This record includes the history and physical examination recorded in minute detail, all routine and special laboratory reports, the complete report of all consultants and roentgen-ray examinations, the final diagnoses, and a final comment in which the reasons for reaching these diagnoses and the suggested treatment are outlined. In addition, abstracts of pertinent articles in the medical literature, prepared by the residents and staff members for the files, are included with many records as they are sent to the referring physician. This is a valuable service not only to the physician who thus has at hand the latest information available to aid him in the management of his problem cases, but also to the staff of the diagnostic hospitals who are stimulated to use the library and to develop the knack of critically filtering important data. Needless to say, the patient is the ultimate beneficiary.

The nature of the diagnostic hospital is such that a variety of unusual cases are continuously available for presentation at staff conferences and other teaching exercises for postgraduate students. A great volume of clinical material valuable for purposes of instruction passes through the hospital and the ambulatory diagnostic clinic. All services are so organized that diagnostic study is completed in a short time. The *average* hospital stay is about four days. Last year approximately 5000 patients were examined. These were referred by over 2000 physicians scattered throughout New England.

There is still another facet of the Bingham Associates Program of continuing medical education for practicing physicians. This is the *Bulletin of the New England Medical Center*. It is a bimonthly publication mailed without charge to graduates of Tufts College Medical School, the staff members of the affiliated hospitals, physicians who have attended postgraduate courses, physicians who have referred patients to the Joseph H. Pratt Diagnostic Hospital and to medical libraries upon request. Others may subscribe for a nominal fee. In the *Bulletin* are included abstracts of the most important papers presented at the morning conferences of the New England Medical Center. Guest speakers from the many hospitals and research laboratories in Boston are invited to conduct these meetings at least once each week. They prepare 1500 to 2000 word summaries of their topics, and these, plus articles, case reports, and teaching abstracts prepared by the staff of the Center make up the contents of the *Bulletin*. Recent developments in many fields can promptly be imparted to the practicing physicians of New England through this medium. Those who have previously attended the morning conferences at the Medical Center particularly appreciate this opportunity of continuing to partake of the benefits of these conferences.

It is obvious from the enthusiastic reception received that in the fields of continuing medical education already explored by the Bingham Associates Program there is fertile ground for improving the medical care enjoyed by the people in a wide area. The construction of costly new hospitals is not an essential part of this program. It is essential, however, to have a medical school base and a broad concept of what is being attempted in order to make available to a large number of general practitioners many of the educational advantages that derive from contacts with teaching institutions.

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CASE REPORTS

SUBACUTE BACTERIAL ENDOCARDITIS PRESENTING AS A SUBARACHNOID HEMORRHAGE (REPORT OF A CASE—WITH RECOVERY) *

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Although subacute bacterial endocarditis is the most common cause of mycotic aneurysms in arteries in various organs throughout the body, including the cerebral vessels, the occurrence of subarachnoid hemorrhage during the course of the disease appears to be a most uncommon event. Stein [1] in 1944 reported a fatal case from South Africa in a colored girl, age nine years. In the same year, Hagerman [2] made the diagnosis in a young married woman, who subsequently died from the endocarditis after surviving the subarachnoid hemorrhage, but this case was not published.

A search through the Quarterly Cumulative Index Medicus from 1932 through 1945 revealed only one published report [3] specifically mentioning the combination. Peculiarly enough, no instance was found in the medical literature of the United States or Great Britain.† Likewise, a study of many standard textbooks unearthed only several scant references to the possibility of subarachnoid hemorrhage occurring in bacterial endocarditis. These included such authors as Osler, Tice, Nelson, Boyd, Cecil, White, Sajous, Lewis, MacCallum, Bing, Purves-Stewart, Wechsler, Meakins, Moore, Kauffmann and Klotz.

This seems particularly strange inasmuch as most of the authorities stress the frequent occurrence of mycotic aneurysms in the cerebral vessels as a result of bacterial endocarditis. Tice [4] says: "Mycotic embolic aneurysms are fairly frequent, especially of the cerebral and meningeal vessels, due to a combination of the infection and toxemia." Alpers [5] states: "Among the secondary causes of subarachnoid hemorrhage is trauma. This is probably one of the most important causes of all. It is also found in syphilis, tuberculosis, blood dyscrasias such as hemophilia and purpura, leukemia, pernicious anemia, scarlet fever, measles, diphtheria, pertussis, acute meningitis and sepsis. *It may be the only manifestation of an embolic process from a subacute bacterial endocarditis.* . . . In subacute bacterial endocarditis, massive cerebral hemorrhage may develop as the result of an infected embolus, which may lodge in a vessel wall, produce an arteritis, aneurysm, and rupture of the vessel. Subarachnoid hemorrhage may

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† Since submission of this manuscript for publication, two reports have appeared in the American medical press. Mallory's [12] case concerned a terminal event in a 50 year-old woman. Paul, Bland and White [13] in a survey of 44 cases of bacterial endocarditis treated with penicillin reported two fatal cases due to subarachnoid and intracerebral hemorrhage resulting from the rupture of a mycotic aneurysm. Their second case is of particular interest as the fatal complication occurred after a four weeks' course of therapy had been terminated with apparently excellent results.

also develop in the same way alone or in association with cerebral hemorrhage, and may be the only cerebral manifestation of the disease. In such cases the hemorrhage in the subarachnoid space is spread widely over the vertex and base of the brain. Hemorrhage into the ventricles may also occur."

Boyd [6] writes as follows: "Vascular lesions, while not so common as embolic manifestations, may produce very striking results. Of these the most important are mycotic aneurysms. The cerebral vessels are the chief sufferers, but such vessels as the superior mesenteric, the femoral and even the aorta may be the seat of such aneurysms. . . . Perhaps the commonest variety of aneurysm at the base of the brain is the embolic mycotic variety, in which the source of infection is a vegetation from bacterial endocarditis." In a personal communication, Boyd [7] reports that a search of his personal files has disclosed two instances of subarachnoid hemorrhage complicating subacute bacterial endocarditis. One of these occurred in a boy of 12 years, the other in a man of 68.

Swift [8] similarly states: "Still another and very important site for the lodgement of small emboli is in the walls of blood vessels, chiefly of the arteries, where they settle either directly on the endothelial lining and from this point set up an inflammation of the vessel wall, or, more frequently they are deposited in vasa vasorum and thus produce focal arteritis of the larger blood vessels. In either event, the wall of the artery is weakened and an aneurysm finally results. As the inflammation progresses, the aneurysm may rupture and this accident then be followed by hemorrhage into important organs; this is not infrequently the cause of death in this disease." Savitsky's [9] short comment is similar to the scant reference found in other books: "Ruptured mycotic aneurysm (at the base of the brain) is known in subacute bacterial endocarditis."

Moore's [10] views on the subject follow: "These (mycotic) aneurysms are extremely thin-walled and usually rupture, bringing about death. They are commonest in the cerebral and in the mesenteric arteries. . . . Mycotic aneurysms are found in about 10 per cent of all instances of this condition (subacute bacterial endocarditis). The aorta is most frequently involved, with the superior mesenteric, hepatic, splenic, cerebral and coronary arteries following in that order."

Perry [11] in his excellent monograph on the disease makes no specific mention of subarachnoid hemorrhage per se, but in his discussion of the "meningeal type" of subacute bacterial endocarditis he cites the case of a 34 year old woman with head retraction, positive Brudzinski's and Kernig's signs, and blood-stained cerebrospinal fluid, in whom the autopsy revealed gross cerebral hemorrhage from rupture of a mycotic aneurysm of the left posterior cerebral artery. He states that such cases would appear to be due to a particularly intense involvement of the meninges and central nervous system by showers of minute emboli.

There is such agreement among medical authorities concerning the frequent development of mycotic aneurysms in the cerebral arteries as a result of subacute bacterial endocarditis, that it seems remarkable that there have been so few instances of reported cases of subarachnoid hemorrhage complicating the disease. It would appear very probable that other cases in the literature may have been published without a reference to subarachnoid hemorrhage within the titles of the articles, and are therefore very difficult to locate.

Owing to the rarity of such a serious cerebral vascular accident in subacute bacterial endocarditis, and more particularly to the fact that the writer has been

unable to find a previously published report of a complete recovery, the history of the following case is herewith presented.

Case Report

A thin young white woman of 22 years of age, employed as a civil servant, was admitted to the public medical service of the Ottawa Civic Hospital on July 12, 1945 in a semi-stuporous state.

The history on admission stated that she had been perfectly well until the day before her entry into the hospital. Early the previous afternoon she had complained of a sense of weakness and malaise. In early morning of the day of her admission, she awakened with a sharp headache over the frontal area, centered above the right eye. This was associated with pain and stiffness in the back of the neck. Vomiting occurred several times during the morning. The headache increased in severity and she became noticeably drowsy. She was brought to the hospital about 12.30 p.m. the same day.

Subsequent interrogation elicited the fact that the original history was in error in declaring that she had been perfectly well until July 11, 1945. In fact, for a period of about six weeks she had felt rather weak and easily fatigued, had had frequent mild headaches and aching discomfort in the legs. Occasionally she had felt slightly feverish and chilly. She had consulted a physician one month prior to admission to the hospital. Nevertheless, she had continued her work despite the symptoms.

Her past history disclosed that she had suffered an attack of acute rheumatic fever at the age of six years. An appendectomy had been performed in 1944, about one year prior to the present illness. Both parents and all five siblings were alive and well.

At the time of admission physical examination revealed a pale, rather undernourished, listless and somewhat drowsy young white woman, who appeared quite ill. Temperature was recorded as 100.2° F., pulse 88, and respirations 20. No changes were noted incident to the examination of the nose, ears and throat. The pupils were equal and quite active, and the ocular muscles were considered normal. Definite neck stiffness was elicited and Kernig's sign was positive. The ocular fundi revealed a slight degree of papilledema bilaterally.

Examination of the heart did not reveal a palpable thrill over the precordium. The apex beat was described as being just medial to the mid-clavicular line. The rhythm was regular and a loud blowing systolic murmur was heard at the mitral area. The systolic blood pressure was registered as 118 mm. of mercury and the diastolic 68 mm. The lungs were clear, and the abdomen was entirely negative aside from the presence of an appendectomy scar. The spleen was not palpated.

Slight muscle tenderness was noted in the calves of the legs, and there was slight discomfort on moving the right ankle. Petechiae were not described. Neurological examination revealed no additional positive findings.

Investigation and Progress of the Case. A lumbar tap was performed on the first hospital day and 15 c.c. of bloody cerebrospinal fluid were obtained, the fluid being identical in all three tubes. The initial pressure was recorded as 290 mm. of water, and the Queckenstedt response was positive. A cell count on this fluid revealed the following: 2 lymphocytes, 104 neutrophiles and 19,000 red blood cells per cubic mm. The total protein was over 700 mg. and the globulin markedly increased. The white blood cell count was 11,350, the red cell count 4,210,000 and the hemoglobin 10.9 grams. A differential count gave the following percentages: neutrophiles, one lobe 4; neutrophiles, two plus lobes 79; lymphocytes 14; and monocytes 3. Urinalysis revealed a specific gravity of 1.020, a faint trace of albumin, no sugar, and a 2+ test for acetone. Amorphous phosphates were the only microscopic finding. The blood Wassermann and standard Kahn reactions were negative. The Wassermann test on a

subsequent specimen of cerebrospinal fluid was also negative, and the colloidal gold curve was reported 0000111222.

During the first 10 days, the patient had a stormy course. The temperature rose to 104° per rectum on the fourth hospital day, and the daily fluctuations for the following week ranged from 99° to 103°. The pulse varied from 72 to 100. Headache persisted for nearly 10 days, as did the neck stiffness. On the eighth day the patient was still sufficiently confused as to get out of bed without authorization.

No further taps were done until the fifth day, at which time bloody fluid was again found. This contained 850 polymorphonuclears, 20 lymphocytes and 30,000 erythrocytes per cubic mm. After the fluid was centrifuged, the supernatant was xanthochromic. On the seventh day the cerebrospinal fluid was frankly xanthochromic and contained 10,000 red blood cells per cubic mm., and on the tenth day it was faintly xanthochromic and the red cell count was 400. On the sixteenth day it was faintly straw-colored and the count was 1,500, with a total protein of 52 mg. On the thirty-fourth day, the last lumbar puncture revealed clear fluid with a count of 9 lymphocytes and 10 red cells, and a total protein of 35 mg. All the specimens of cerebrospinal fluid were sterile on culture.

From the twelfth to the twentieth days the oral temperature varied from 99.4° to 103° F. daily, and from then until the fortieth day it ranged from 98.8° to 101°. From the fortieth to the forty-eighth days it was slightly higher—99° to 102.2°. During this phase of her illness, the patient felt much better than during the first 10 days but did complain of malaise, anorexia, dyspnea and sweating. The first blood culture was done on the forty-fourth day, and the laboratory reported a growth of non-hemolytic streptococci after four days' incubation. This was confirmed by a second culture done on a specimen of blood taken one day after the first one.

Sulfadiazine therapy was commenced on August 24, 1945, and within 36 hours the temperature dropped to normal for the first time since the admission to hospital. Because the leukocyte count dropped to 3,700, the sulfonamide was discontinued after four days' administration. The patient remained afebrile for five days except for three recordings of 99°.

This was the situation as it existed when the patient first came under the observation of the author on September 1, 1945, the fifty-second hospital day. It was then apparent that the young lady had recovered from a clear-cut subarachnoid hemorrhage, and that the cause of the persistent fever was almost certainly a subacute bacterial endocarditis. At this time a definite thrill was palpable over the mitral area. There was a very diffuse and forcible apex beat which extended beyond the mid-clavicular line. A loud systolic murmur could be heard most intensely at the apex, and a faint apical diastolic murmur was also detected. The pulse rate was now ranging from 100 to 132, always with a regular rhythm. The spleen was definitely just palpable, but no petechiae could be discerned. Several urinalyses at this time did not reveal microscopic hematuria. It was then decided to withhold further therapy until a sharp rise in temperature recurred and until after another specimen of blood could be taken for culture at the peak of the fever.

Fortunately, the delay was of very short duration as on September 3, 1945, the fifty-fourth day, the patient suffered a chill with a rise in temperature to 104°. After 24 hours, the culture revealed an organism which appeared to be a non-hemolytic streptococcus, and after three days' incubation it was readily identifiable as *Streptococcus viridans*. Penicillin therapy was started by continuous intramuscular drip immediately after the blood culture had been taken on the fifty-fourth day in a dosage of 300,000 units per day. When the laboratory report suggested that the organism was extremely resistant to penicillin, the dose was promptly increased to 500,000 units and this was continued daily for four weeks. The total dose of penicillin employed was 12,300,000 units. Despite the exceedingly pessimistic laboratory prog-

nosis concerning the resistance of the organism, the patient's temperature fell to normal levels within 48 hours where it consistently remained, aside from very occasional readings of 99°, from the fifty-sixth day until her discharge from hospital on the one hundred and fourth day. Blood cultures were reported sterile on the sixty-eighth, seventy-fifth, and one hundred and first days.

Uninterrupted improvement continued in the patient's general health, and she was allowed out of bed on October 13, 1945, the ninety-fourth day. At this time her leukocyte count was 4,750, the red cells numbered 5,360,000, and the hemoglobin was 12.4 grams. A roentgenogram of the chest on October 17, 1945 revealed slight cardiac enlargement (figure 1), which was not apparent on an earlier film taken two months previously. An electrocardiogram taken on August 28, 1945 revealed abnormal findings in the third standard lead only, the S T interval being bowed upwards slightly and the T-wave inverted (figure 2).

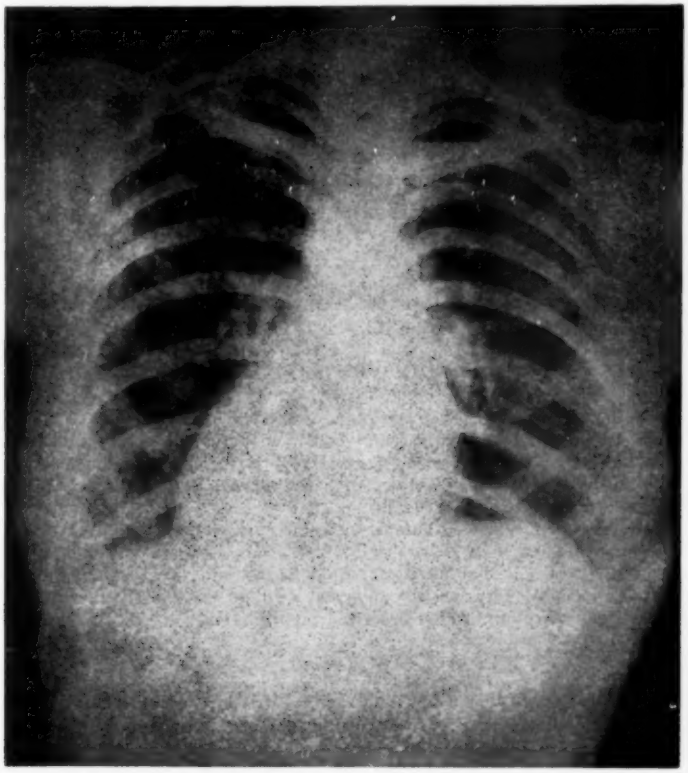

FIG. 1. Roentgenogram of the chest, Oct. 17, 1945. "The lungs show good illumination. There are relatively heavy root shadows on both sides. The diaphragms are clear. The heart shadow is moderately large. The cardiothoracic ratio is 13.5/26.5. The aortic shadow is not enlarged. Conclusions: There is slight enlargement of the heart, with fairly heavy hilar markings. When compared with a chest film of August 13, 1945, the earlier roentgenogram disclosed normal root shadows and a normal cardiothoracic ratio of 12/26."

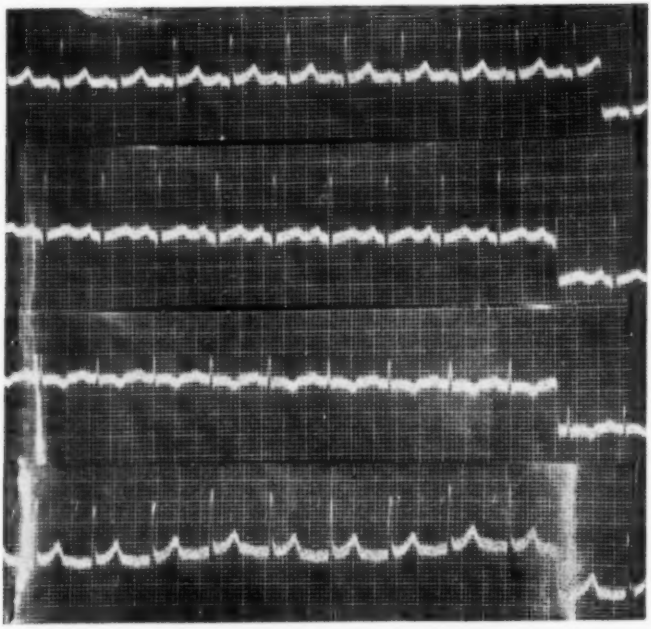

FIG. 2. Electrocardiogram, Aug. 28, 1945. "Regular sinus rhythm, rate 100. Conduction time .16 second. QRS complexes normal, no axis shift. In Lead III, the S T interval is bowed upwards slightly and the T-wave is inverted."

The patient was discharged in good condition on October 23, 1945. Very shortly thereafter she departed for her parental home in Western Canada to undertake a prolonged period of convalescence. Several reports were received from her local physician during the year she remained in Saskatchewan, and they revealed that she had continued to enjoy excellent health.

Shortly after her return to Ottawa to resume her work in the civil service, she appeared for examination on November 23, 1946. She had no complaints other than occasional slight fatigue and infrequent mild palpitation. There were no physical findings aside from the very harsh systolic and the faint diastolic murmur at the apex of the heart, indicative of mitral stenosis and regurgitation.

DISCUSSION

As previously mentioned, a rather thorough study of the medical literature leads to the conclusion that, while mycotic embolic aneurysms of the cerebral vessels occur quite frequently in cases of subacute bacterial endocarditis, the occurrence of subarachnoid hemorrhage is an exceedingly rare complication during the course of this disease.

It is, however, interesting to postulate that in the future some cases of subarachnoid hemorrhage may develop in individuals who have recovered from subacute bacterial endocarditis following treatment with penicillin. It would seem

inevitable that some of these cured cases will harbor residual mycotic aneurysms in their cerebral vessels, and that they will remain forever as possible sources of subarachnoid or cerebral hemorrhage. Physicians should, therefore, keep in mind the possibility of such a sequel in connection with cases who have been cured of this erstwhile fatal disease.

The recovery of this reported case was particularly gratifying in view of the marked resistance of the organism to penicillin when tested in the laboratory. While the dosage of the drug utilized in the treatment of this case seemed quite large at that time, it is certain that now, under similar circumstances, the amount of penicillin which would be advocated would be at least two or three million units daily.

Summary and Conclusions

1. While mycotic cerebral aneurysms are commonly found in cases of subacute bacterial endocarditis, very few instances of subarachnoid hemorrhage complicating this disease have been reported in the literature.

2. It is suggested that subarachnoid hemorrhage may be reported in the future as a late sequel in cases of subacute bacterial endocarditis cured by penicillin therapy.

3. The history of a case of subacute bacterial endocarditis presenting as a subarachnoid hemorrhage is described, in the belief that this constitutes the first published report of a complete recovery from such an occurrence.

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ERYTHEMA MULTIFORME BULLOSUM DUE TO SULFADIAZINE SENSITIVITY CONTROLLED WITH PROCAINE INTRAVENOUSLY *

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THE development of a skin eruption following the use of sulfonamides does not as a rule present a difficult therapeutic problem, since in most instances the rash clears up with the cessation of the chemotherapy. Additional benefit may also be obtained from the use of epinephrine or the antihistaminic drugs. There are, however, instances of sulfonamide eruption in which the routine measures are of no avail. In the case herein reported the rash did not respond to the standard forms of treatment but cleared up promptly following the intravenous administration of procaine.

CASE REPORT

B. M., a colored male, aged 30, was admitted to Sydenham Hospital on November 8, 1947, with the complaints of chills, fever, a skin eruption composed of hives and blebs, and marked pruritus of four days' duration. These symptoms developed two hours following the ingestion of 0.5 gram of sulfadiazine, which he mistook for a "headache pill." The past history was relevant since in 1941 he manifested the first episode of sulfonamide hypersensitivity, namely the development of pruritus 24 hours following the ingestion of an unknown dose of sulfanilamide. In 1946 pruritus and fever appeared three hours after taking one gram of sulfapyridine. A more intense reaction consisting of pruritus, fever and a bullous eruption occurred in October, 1947, three hours following the use of one gram of sulfadiazine. These previous episodes of drug sensitivity were of relatively short duration and cleared up spontaneously. In the present episode some measure of temporary relief was obtained at first in the Clinic from the combined use of phenobarbital, adrenalin and benadryl. Soon, however, the symptoms recurred with increased severity and failed to respond to this medication. Consequently, the patient was forced to seek admission to the hospital.

On admission the patient appeared acutely ill and in marked distress. The temperature was 99° F., the pulse rate 82 and the respiratory rate 22. The blood pressure was 115 mm. of mercury systolic and 78 diastolic. There was generalized edema of the face. The lungs were clear and the heart appeared normal. The spleen was not felt but hard and tender lymph nodes were present in both inguinal regions. The most striking finding was the involvement of the skin, which revealed a polymorphous eruption over the entire body, including the extremities and genitalia. There were numerous ebony colored macular areas ranging in size from one to five centimeters and slightly raised bullous lesions on an erythematous base which varied from two to six centimeters in diameter. In addition, large circumscribed urticarial lesions covered the back, lower abdomen and extremities. There was no involvement of the mucous membranes. The neurological examination was entirely negative.

The urine had a specific gravity of 1.008, was negative for albumin and sugar and showed a 2 plus urobilinogen and an occasional white blood cell. There were 4,950,000 red blood cells with 97 per cent hemoglobin and 7,800 white blood cells with a differential of 61 per cent polymorphonuclears, 32 per cent lymphocytes, 2 per cent eosinophiles and 5 per cent monocytes. Serological tests for syphilis were negative.

* Received for publication September 7, 1948.

Since the routine measures applied prior to admission had failed to alleviate the patient's condition, it was decided to institute procaine therapy at once. Five grams of procaine hydrochloride diluted with 1,000 c.c. of isotonic solution of sodium chloride were administered intravenously over a period of four hours. Complete subjective relief was obtained within 15 minutes after starting the infusion. At the end of one hour there was considerable reduction of the urticaria and facial edema and marked general improvement. By the time the infusion was completed there were no skin lesions, except for flattened bullae which subsequently dried up. No untoward reactions followed the use of procaine. The patient made an uneventful recovery and was discharged in excellent condition on the sixth hospital day.

Before discharge from the hospital the patient was subjected to sulfonamide skin tests. He received one intradermal injection of 0.05 c.c. of 1 per cent solution of sulfapyridine and another injection of 0.05 c.c. of a .75 per cent solution of sulfadiazine. Fifteen minutes following these injections, an irregular wheal measuring about 5 centimeters in diameter appeared at the site where the sulfapyridine was introduced and a slightly smaller reaction was noted over the sulfadiazine area. A control individual who was tested similarly showed no reactions.

Comment

There can be little doubt that the patient's symptoms were on the basis of drug allergy, especially in view of his past history of sulfonamide sensitivity. Additional confirmation was obtained from the positive skin tests. It is necessary to mention, however, that the demonstration of sulfonamide sensitivity by the ordinary intradermal procedure is very unusual.

Of particular interest is the patient's dramatic response to procaine. The value of this drug in the treatment of serum sickness has already been reported on by State and Wangensteen [1] and by Appelbaum, Abraham and Sinton.[2] The excellent results obtained from the use of procaine in the case herein described illustrate the value of this agent in the treatment of hypersensitivity due to sulfonamides. It may be important to note that the dosage of procaine used in this case was higher than that originally recommended by State and Wangensteen.[1] This may suggest the advisability of using larger doses of the agent to control the more severe manifestations of hypersensitivity.

The exact mode of action of procaine in the treatment of hypersensitive states is at present unknown. State and Wangensteen [1] suggested several explanations for the action of this anesthetic agent, namely direct action on the cells, antihistamine effect, antiacetylcholine action and epinephrine potentiation. In this connection it is of interest to note that procaine is chemically related to benadryl and other antihistaminic drugs. This relationship is emphasized in a paper by Peterson and Bishop.[3] The recent experiments by Shanes [4] which demonstrated that cocaine reduces membrane permeability to potassium, may shed further light on the mode of action of procaine.

Summary

We have reported a case of erythema multiforme bullosum due to sulfadiazine sensitivity, in which positive sulfonamide intradermal tests were demonstrated. The rash did not respond satisfactorily to the standard forms of treatment, including the use of benadryl, but cleared up promptly following the intravenous administration of procaine.

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ANGINAL SYNDROME DURING SODIUM SUCCINATE THERAPY *

By CLEMENT S. DWYER, M.D., SANFORD KRONENBERG, M.D., and MEYER SAKLAD, M.D., *Providence, Rhode Island*

THE introduction into experimental clinical medicine of agents which take part in the oxidation-reduction systems of the body has stimulated the interest of clinicians in tissue metabolism and its mechanisms. Succinic acid salts have been discussed in the literature from the standpoint of their effects on oxidative processes in vitro and in the living animal. Various investigators are studying their possible application in the treatment of certain conditions, notably barbiturate intoxication and anesthesia,[1, 2, 3, 4, 5, 6] hypoxia,[7, 8] and rheumatic fever,[9] but the bibliography pertaining to their use is still meager.

Comprehensive evaluation of such agents requires a long period of time, and contributions from many sources of investigation are needed. In dealing with a new drug one must consider, in relation to the therapeutic action and benefits desired, such factors as the route of administration, concentration, dose, pharmacological side-effects, and individual idiosyncrasies.

One hesitates to point out deleterious side-effects of a new drug, while at the same time collecting evidence to support its use. It is a truism that the report of an untoward reaction can be completed at any time, while an accurate and critical evaluation of a drug or technic must await the collection of a mass of favorable data. We believe, however, that unfavorable reports should find their way into the literature at an early date so that other observers may benefit from them. It is hoped that the casual reader will not formulate a biased opinion of an agent from a single case report.

Sodium succinate has been administered on the medical and surgical services of our hospital. On several occasions it was given to patients who had intermittent claudication. The results warranted its continued trial. One of the patients developed symptoms of severe angina pectoris during the injection of the drug. Her case history is herewith presented.

* Received for publication February 21, 1947.
From the Rhode Island Hospital, Providence.
The sodium succinate (Soduxin) used in this study was supplied through the courtesy of Brewer & Co., Inc.

Case Report

A 65-year-old Russian-Jewish female was admitted to the hospital with a diagnosis of arteriosclerotic peripheral vascular disease.

Chief Complaint. Severe pain in both lower extremities on walking or standing.

Present Illness. For one year, the patient had noticed severe, cramp-like pains in the calves of both legs and numbness of the toes on walking a short distance or after standing for a short time. The pain was more severe on the right side. At the time of admission she could walk no further than 20 feet without the onset of cramps. Similar pains frequently came on at night when she was in bed. Her symptoms had become progressively worse until she was unable to do routine housework.

Past History. Three years ago, at the time of the death of a relative, she had an acute episode of substernal pain and oppression which persisted for only a few minutes. Radiation of the pain was not noted. Since then she had had occasional recurrences of the feeling of oppression during emotional upsets. There was usually subjective difficulty in breathing associated with this complaint.

Intolerance to fatty food and eggs, epigastric and right upper quadrant discomfort relieved by the ingestion of alkali, and other gastrointestinal symptoms had been diagnosed as due to chronic cholecystitis.

Review of the systems revealed no other relevant complaints.

Physical Examination. The patient was a well-developed and well-nourished elderly woman in no distress. Oral temperature was 97.6° F., the pulse was 96 and the respirations were 22. Her blood pressure was 150 mm. of mercury systolic and 80 mm. diastolic. Percussion and auscultation of the lungs revealed no abnormal findings. The heart was not enlarged to percussion. Its rhythm was regular. The sounds were distant and there was a soft systolic murmur at the apex. Examination of the abdomen was negative. There were varicosities of the lower extremities. The skin of both feet was pale and cool. No tenderness was elicited in the extremities. Pulsations in both femoral arteries were decreased, more so on the right, and popliteal and dorsalis pedis pulsations were absent bilaterally.

Laboratory Findings. Hemoglobin: 14.6 gm. White blood cell count: 7,450. Differential count: polymorphonuclears, 60 per cent; lymphocytes, 34 per cent; monocytes, 6 per cent. Urine: negative. Oscillometric tracings showed diminished pulsations in both thighs and absent oscillations in right calf, ankle, and foot.

On the day of admission she was able to take only 10 steps before cramps and numbness occurred in the right leg. That afternoon 10 c.c. of 30 per cent sodium succinate (Soduxin) were slowly injected into the left median basilic vein. Shortly after the beginning of the injection, an abrupt spell of coughing began. This is a usual occurrence with this drug. The patient complained of a taste of sulfur and a feeling of coolness of the left hand. She described a fullness in the throat, a generalized feeling of warmth, a feeling of pressure across the upper abdomen and lower chest, and difficulty in breathing. These symptoms subsided when the injection was slowed but recurred when the speed of the injection was increased. Dizziness was present during the injection and for about 10 minutes thereafter. Her blood pressure was 160/80 before the injection and 185/70 immediately after the injection. The pulse remained unchanged at 80.

As soon as the dizziness had disappeared she was able to walk a distance of 400 feet, and would have continued had not general fatigue prevented the completion of the test. There was no pain in the calves at any time after the injection. She remained out of bed, walking about at will for the rest of the day. Her mental attitude was improved. She appeared bright and cheerful, and stated that for the first time in many months she was able to walk without discomfort.

A second dose of sodium succinate was given on the afternoon of the following day. It was felt that a more dilute solution, given over a longer period of time, might

make the injection more pleasant for the patient. An ampoule of Soduxin, containing 3 gm. of sodium succinate, was diluted with 250 c.c. of 5 per cent glucose in distilled water and started into the right median basilic vein by continuous drip. The infusion was begun at 110 drops per minute. After a brief period, corresponding to that of the previous day, there was an abrupt recurrence of the symptoms of coughing, restlessness, fullness in the throat, tasting of sulfur, and generalized warmth. Respirations were deeper and she appeared to be having mild respiratory distress. The infusion was slowed to 70 drops per minute and all of these symptoms disappeared. The patient then complained of marked dryness of the mouth. The rate of flow was gradually increased to 110 drops per minute over a period of 10 minutes and, except for dryness of the mouth, there were no complaints. Twice during the next 40 minutes, when the rate was momentarily increased to 150 drops per minute, there was an immediate recurrence of the same symptom complex, with a feeling of pressure in the anterior chest. After 200 c.c. had been given she began to complain of slight heaviness in the midsternal area, although the rate of flow was still 110 drops per minute. The infusion was slowed to 60 drops per minute. The feeling of heaviness, however, became progressively worse. The infusion was discontinued but the patient began to complain of sharp pain localized at the midsternum. Seven minutes later, 0.3 mg. of nitroglycerin was administered sublingually and within a minute the substernal distress was relieved.

About 30 minutes later the pain recurred with increased severity and radiated down the dorsum of the left arm to the wrist. The patient appeared quite appre-

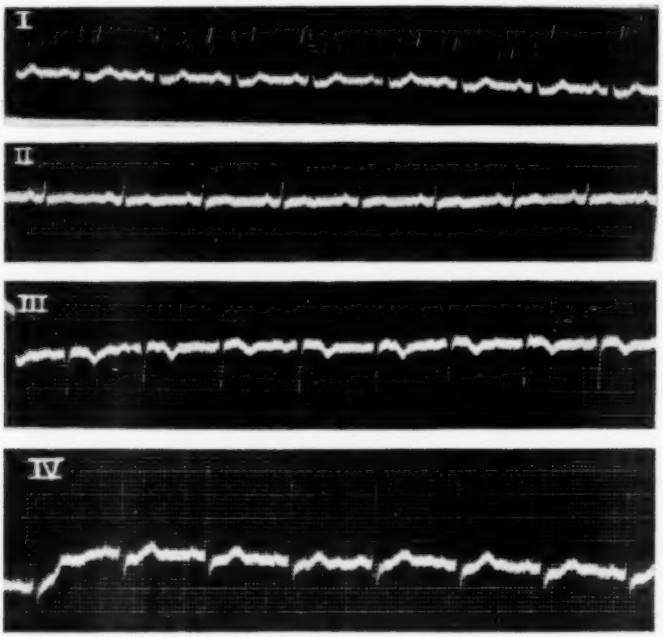

FIG. 1.

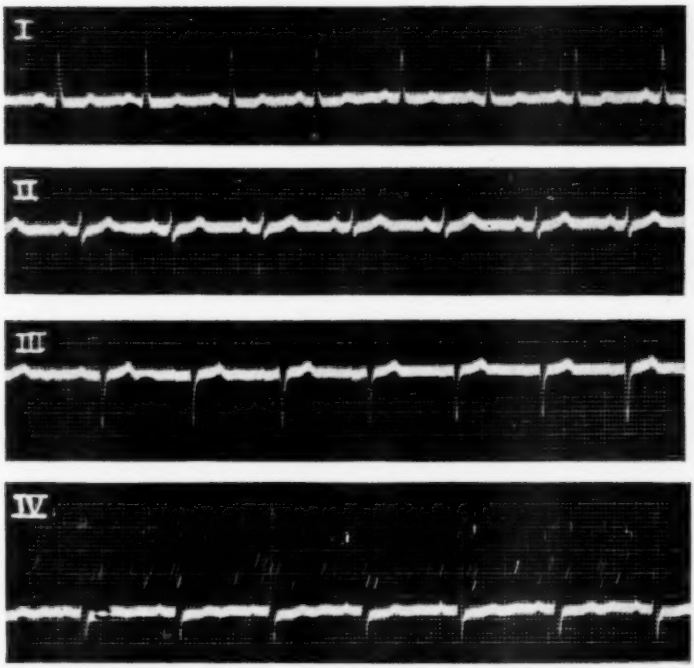

FIG. 2.

hensive and pale. The skin of her forehead was damp and cool. Her blood pressure was 200/90 and her pulse was 70. The intravenous injection of 0.25 gm. of aminophyllin brought about immediate alleviation of pain. Mild discomfort persisted in the chest and arm for three to four hours. She vomited during the injection, and felt nauseated during the rest of the day and night. The report of an electrocardiogram taken that afternoon (figure 1) read as follows: "The tracing shows a normal sinus rhythm. T_3 is inverted. There is slight sagging of the ST interval in Lead I. The chest leads show normal QRS complexes with slight depression of the ST interval, most evident in CF_4. The limb leads show no clear abnormality. The depression of the ST interval in the chest lead is suggestive of coronary insufficiency, but its significance will depend on the findings in subsequent tracings. The rate is 80." Early in the evening there was a recurrence of the severe pain. It was relieved by the administration of 0.5 gm. aminophyllin intramuscularly.

On the following morning the patient had no complaints except for slight nausea. Her color was improved and she had no discomfort. That afternoon, while at rest in bed, the patient experienced another episode of severe substernal pain radiating into the left arm. Oxygen was administered by nasal catheter and the pain was alleviated. Five days later the patient was up and about the ward. Discomfort in the chest and cramps in the legs did not recur. An electrocardiogram taken on the ninth hospital day (figure 2) was interpreted as follows: "The tracing shows a normal sinus rhythm. Rate 78. The pulse waves and QRS complexes are unchanged from the record of five

days ago. In today's tracing, T_2 and T_3 are still upright. The chest lead is unchanged. The changes since the previous record are in T_2 and T_3. The changes in the T waves are difficult to explain but may represent temporary myocardial insufficiency in the previous record."

The patient was discharged on the tenth hospital day.

Comment

This case is of interest because of the fact that the intravenous injection of sodium succinate brought about relief of intermittent claudication due to arteriosclerosis and, at the same time, precipitated attacks of angina pectoris.

A therapeutic trial of intravenous hypertonic sodium chloride solution was not carried out in this patient. Since a control solution was not administered, it is difficult to say that psychogenic factors did not play a part in alleviating the complaints referable to the lower extremities. However, during the 10-day period of hospitalization following the initial injection of sodium succinate, she experienced no cramps or discomfort in the legs.

The diagnosis of angina pectoris was borne out by the typical clinical picture which the patient presented at the time of the severe chest pain. Electrocardiographic tracings taken while symptoms still persisted and again after all symptoms had disappeared showed changes which substantiate the assumption that there were ischemic myocardial disturbances. Immediate alleviation of pain by nitroglycerin and aminophyllin and the efficacy of oxygen inhalation lend further support to the diagnosis. Vomiting, beginning abruptly during the first injection of aminophyllin, may have been due to myocardial insufficiency, pain, or to the aminophyllin, probably the last.

A review of the patient's history raises the question whether emotional disturbances may have played a major rôle in the production of the anginal syndrome. It is possible that the unpleasant symptoms resulting from the injection of sodium succinate disturbed the patient sufficiently to precipitate a coronary artery spasm. However, there appeared to be a direct relationship between the rate of injection and the onset of midsternal oppression, the latter coming on precipitously when the flow was speeded and disappearing when it was slowed. The most severe attack of typical anginal pain in the chest and arm came on when accompanying symptoms were absent and after the greater portion of the second infusion had been given.

It is difficult to conceive of a mechanism whereby sodium succinate might bring about relief of the discomfort associated with intermittent claudication and, at the same time, be responsible for pain due to myocardial ischemia. This seems to have been the case in this patient. Ten days after her discharge from the hospital she was still entirely asymptomatic.

Summary

We have presented the case report of a patient in whom intravenous sodium succinate (Soduxin) appeared to bring about relief of intermittent claudication due to arteriosclerotic peripheral vascular disease and to precipitate attacks of angina pectoris. The mechanism for the apparently contradictory effects of the drug is not understood.

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BOECK'S SARCOID: A CASE OF SARCOIDOSIS COMPLICATED BY PULMONARY EMPHYSEMA AND COR PULMONALE*

By Irving Zimmerman, M.D., and Norman Mann, M.D., *New York, N.Y.*

The course of Boeck's sarcoid has in the past been considered relatively benign and free from constitutional symptoms. The increasing number of cases coming to the autopsy table, however, continues to shed new light on the subject and forces one to regard the ultimate prognosis with less optimism than formerly. Rubin and Pinner [1] state that approximately half of the autopsied cases died as a direct consequence of the disease, if one considers caseous tuberculosis as a natural development of Boeck's sarcoid. Although chronic cor pulmonale has been mentioned in the literature as a possible complicating factor secondary to the pulmonary changes, very few well-established cases of this nature have been reported. We are reporting the following case because of the severe pulmonary emphysema and consequent right heart failure that resulted from extensive pulmonary sarcoidosis. The case is interesting since we can demonstrate the roentgenological changes that occurred in the patient's chest over a period of 10 years.

Case Report

E. H., a 21 year old colored boy, was admitted for chronic care to Goldwater Memorial Hospital on June 19, 1946 from another New York hospital, with a diag-

* Received for publication April 16, 1947.
From the Department of Pathology, Goldwater Memorial Hospital, New York, N. Y.

nosis of pulmonary fibrosis, emphysema and cor pulmonale. The only family history of significance was the death of his sister of cavernous pulmonary tuberculosis in 1936. In 1934 a roentgenogram of his chest, taken when his sister was ill, showed no abnormal findings. At Bergen Pines Hospital in New Jersey he again had a chest roentgenogram in July 1936, following the onset of complaints of cough, dyspnea, fatigue, anorexia and weight loss. At that time the film showed markedly enlarged hilar glands and peribronchial infiltration in both the middle third of the left lung and in the right lower lung field. He also had a generalized lymphadenopathy, especially of the cervical glands. Physical signs in the chest at that time consisted of crepitant râles in the right lower lung field and over the left apex. Within the two weeks after admission two tuberculin tests were negative. The tuberculin test, however, later became positive. Bronchoscopy in September revealed nothing of significance. A biopsy of a cervical lymph node was done six months after admission and a diagnosis of tuberculous adenitis was made. No tubercle bacilli, however, were found in the histological section. An axillary node broke down 10 months after admission and was said to have drained caseous material. This was cultured and revealed acid-fast bacilli. Many studies of the sputum and gastric analyses were continually negative for acid-fast organisms. Roentgen films of the hands exhibited no abnormalities. In October 1937, after 15 months of hospitalization, he left against advice. A roentgenogram taken at this time showed only a slight decrease in the size of the mediastinal shadows and degree of peribronchial infiltration. For the next nine years the patient was not followed by any physicians. However, on May 13, 1946 he was admitted to the wards of a New York Hospital because of dyspnea on exertion, which the patient stated had become progressively worse in the preceding three years. During the two month period before admission he had developed a cough productive of approximately one cup of foamy brown sputum daily. Several days prior to admission he had noted swelling in the ankles. Physical examination at the time revealed a markedly cyanotic and dyspneic young negro male. His blood pressure was 120 mm. Hg systolic and 70 mm. diastolic. There was moderate distention of the veins of the neck. Respiration was accomplished by movements of the upper chest and accessory muscles. There was practically no movement of the diaphragm. The lungs were markedly emphysematous. The point of maximal impulse of the heart was felt 11 cm. to the left of the midsternal line in the fifth intercostal space. There was a regular sinus rhythm and no murmurs were heard. The liver was palpated 6 cm. below the right costal margin. The spleen was not felt. A 2+ sacral edema was present. Slight curving of the fingernails, but no clubbing, was noted. A roentgenogram of the chest showed hyperradiable lung fields and accentuation of the pulmonary conus. Fluoroscopy showed very limited movement of the diaphragm. Pulmonary function and blood studies revealed the following information:

Complementary air	860 c.c.
Reserve air	560 c.c.
Residual air	2344 c.c.
Maximal breathing capacity	11 liters per minute
Carbon dioxide content of arterial blood	54 volumes %
Oxygen content of arterial blood	18.3 volumes %
Oxygen saturation of arterial blood	74.5 volumes %
Blood volume	5,500 c.c.
Hematocrit	60%
Red blood cell count	7,000,000 per cu. mm.

Cardiac catheterization showed marked hypertension of the lesser circulation. The patient was digitalized, with slight improvement resulting. Mercurial diuretics, however, produced great diuresis and relief of pulmonary congestion and liver tender-

ness. At this time he was admitted to Goldwater Memorial Hospital for chronic care.

On admission to this hospital, the patient presented essentially the findings described previously. Additional laboratory findings revealed 5,800,000 red blood cells per cu. mm. The hematocrit was 43 per cent. The serum proteins were 5.8 gm. per cent, with an albumin globulin ratio of 2.5/3.3. Circulation studies showed a decholin arm-to-tongue time of 16 to 18 seconds and a venous pressure of 16 cm. of water. The vital capacity was 850 c.c., and 1100 c.c. after Vaponephrine spray. An electrocardiogram (figure 1) revealed a right ventricular strain pattern with high P waves in the second and third leads characteristic of right auricular enlargement. Sputum examinations were negative for acid fast organisms. Guinea pig inoculation of sputum also proved to be negative for tubercle bacilli. Roentgen films of the hands taken here were again normal.

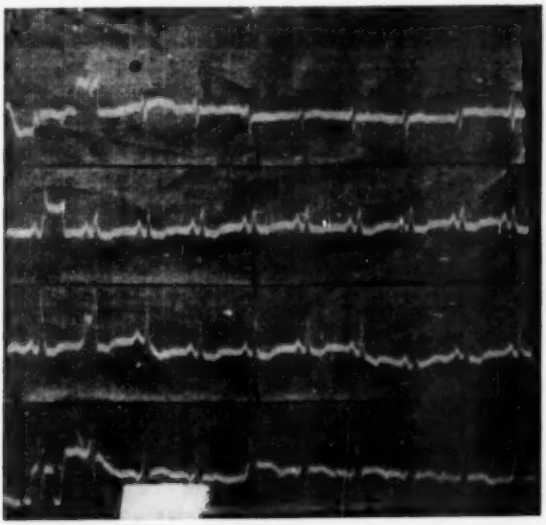

FIG. 1. Right ventricular strain pattern with high P waves in Leads II and III characteristic of right auricular enlargement.

The patient was continued on digitalis while at this hospital. His heart rate throughout his hospitalization was consistently rapid, varying from 100 to 115 per minute. He did not improve to any great extent until the vigorous application of mercurial diuretics and urea was employed. His status thereupon improved so much that at the time of his death, he was receiving mercupurin every four weeks, whereas on admission he had received the drug every four days. Despite this, the patient was quite dyspneic intermittently; an emphysema belt appeared to afford moderate relief. However he gradually became addicted to his oxygen which he used continuously at low pressures. The patient, as noted previously, had a moderately productive cough and also a postnasal drip. A consultation revealed the presence of a right maxillary sinusitis which was treated, with some resultant improvement in respiration. At one time he had a bilateral bronchopneumonia which responded remarkably well to peni-

cillin. His spleen, which was barely palpable on admission, progressively enlarged, to two fingers below the costal margin. Shortly before death his vital capacity was 1,100 c.c., and 1,300 c.c. after Vaponephrine. Approximately six months after admission, on December 16, 1946, the patient suddenly developed a paranoidal mania, presumably secondary to the chronic oxygen deficiency that existed, and went into shock. He died shortly thereafter. An autopsy was performed.

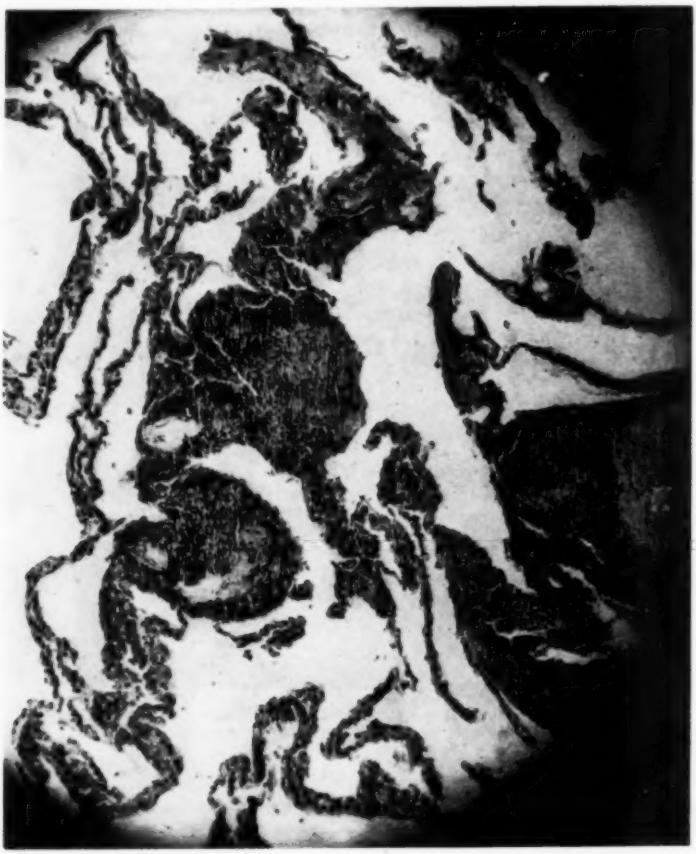

FIG. 2. Section of the lung showing emphysema and several sarcoid lesions.

Pathologic Findings. Examination revealed no abnormalities in the brain. The lungs exhibited marked diffuse emphysema. Each lung weighed approximately 350 gm., and presented a pale blackish-pink appearance. The lungs were light, fluffy, of cotton consistency, and resisted compression. Small bullae were visible in various regions. The cut sections revealed a yellowish-white dry surface in all lobes, except at the bases where there was moderate congestion. There were no areas of infiltration

or consolidation noted. The bronchial tree revealed in all lobes of each lung a slight to moderate tubular bronchiectasis. The pulmonary arterial vessels exhibited moderate atherosclerosis. The diaphragm was at the level of the seventh rib. The heart was in normal position and weighed 455 gm. In its postmortem position the anterior surface was formed primarily by the right ventricle and the right auricle; the left ventricle formed a much smaller portion. Both the right auricle and the right ventricle were markedly dilated and hypertrophied. The wall of the latter was three times normal thickness, measuring 1.2 cm. The left ventricle was slightly dilated and of normal thickness. The findings were typical of chronic cor pulmonale. No other significant findings were observed in the heart. The liver extended several fingers below the right costal margin but was of normal size. The surface was brown, with occasional small yellowish points studded throughout. Cut sections revealed a

FIG. 3. Microscopic section of lymph node biopsied in January 1937.

firm yellowish brown surface. There was a slight suggestion of nodularity. The spleen was markedly enlarged, weighing 330 gm. It was firmly adherent to the underside of the diaphragm and was quite firm to touch. Cut sections revealed a firm red surface on which small speckled white areas were diffusely scattered. The kidneys were not abnormal grossly. As for the lymphatic system, the only gross finding of significance was an enlarged node along the greater curvature of the stomach, which on cut section exhibited a whitish-black surface. The remainder of the autopsy was not significant.

Microscopic sections of the lungs (figure 2) revealed the pleura to be slightly thickened and fibrotic. The alveolar spaces varied considerably in size. Many were very greatly distended. The continuity of the alveolar septae was disrupted in the

areas where the alveoli were most distended. Many small granulomatous nodules were seen in the interstitial connective tissue and in some of the alveolar septae. These granulomas consisted primarily of collections of large mononuclear cells resembling epithelioid cells. Surrounding these were thick mantles of lymphocytes. An occasional giant cell was present. Between the epithelioid cells and the lymphocytes, in some areas, bands of hyaline material were evident. Similar bands were seen within the lymphocytic collections. The bronchioles exhibited a markedly hyperplastic mucosa with infiltration of the wall by round cells. The pulmonary arterial

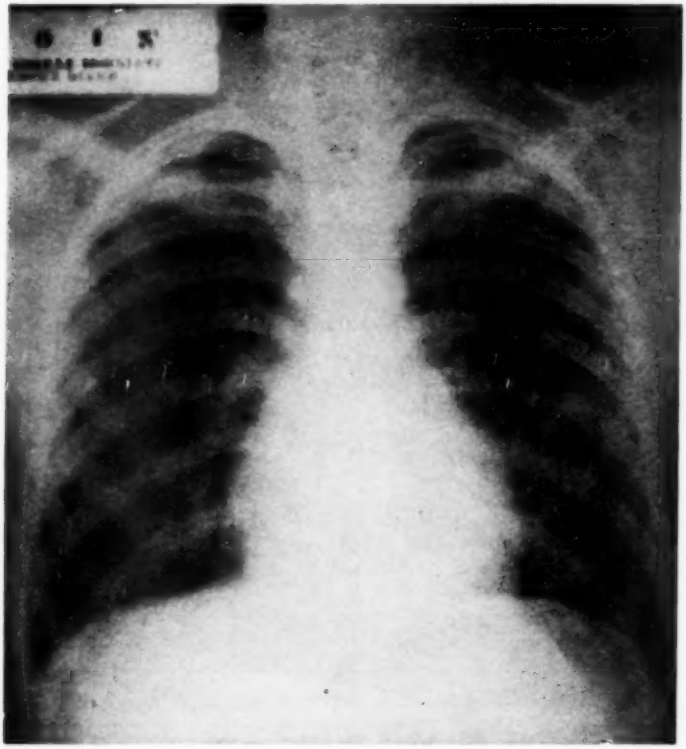

FIG. 4. Roentgen-ray of chest taken in 1934 showing no pulmonary or cardiac lesions.

vessels showed marked thickening of the intima and many lipoid deposits were visible here. No areas of caseation were found in the pulmonary tissue. The acid fast stains of the lung revealed no tubercle bacilli. A diagnosis of Boeck's sarcoid was made. There were granulomatous nodules similar to those in the lungs found diffusely distributed in the liver, spleen and lymph nodes. The kidney sections and also those of a hilar lymph node revealed several areas of hyalinized collagen which were interpreted as healed lesions of sarcoidosis. Sections of the heart showed marked hypertrophy of the muscle fibers of the right ventricle but no sarcoid lesions.

The brain was also free of microscopic lesions. The sections of the biopsied lymph node diagnosed at Bergen Pines Hospital as tuberculous adenitis were obtained and reviewed in our laboratory. It is the consensus of opinion here that the lesions are those of Boeck's sarcoid (figure 3).

Comment

The etiology of sarcoidosis remains unknown, but numerous observations have indicated a close relationship between this disease and tuberculosis.

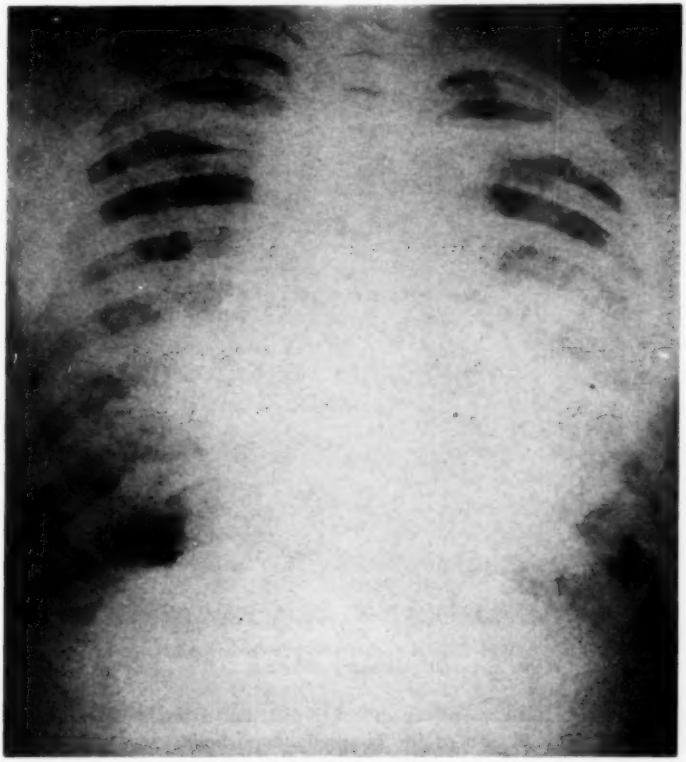

Fig. 5. Roentgen-ray of chest taken in July 1936 revealing extensive infiltration of both lungs and enlarged hilar lymph nodes.

Much of this is based upon the close similarity of the pathologic lesions of the two diseases. Furthermore, Warfvinge [2] in 1943 was able to produce what were considered typical histological sarcoid lesions in a patient with both tuberculosis and Boeck's sarcoid by the injection in the skin of a suspension of her own tubercle bacilli. Pinner [3] and others believe that sarcoidosis is actually a type of non-caseating tuberculosis, dependent upon an atypical reaction to the tubercle

bacillus or its products. According to this concept, sarcoidosis is explained as a hematogenous tuberculosis which develops in an individual whose resistance is high. The latter is thought to be responsible for the mild constitutional symptoms, the absence of tissue necrosis, and destruction of tubercle bacilli in the lesions. The anergy to tuberculin which is so characteristic of sarcoidosis is also considered to be due to the atypical response in these patients. The case presented above is suggestive of the etiologic relationship between Boeck's sarcoid and tuberculosis.

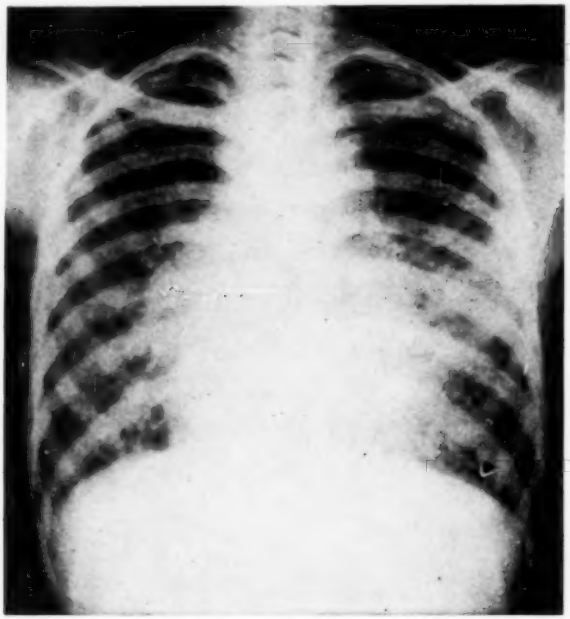

FIG. 6. Film taken in October 1937 at time of patient's discharge from hospital. Large hilar nodes and some pulmonary infiltration still present.

The histologic features of the diffusely distributed lesions exhibited at the postmortem table and also of the biopsied lymph node, consisting of cellular granulomas which rarely contained giant cells, and exhibiting no areas of caseation, were characteristic of sarcoidosis. Another feature frequently seen in this disease was the peculiar hyalinization of the nodules described previously. The minimal fibrosis and absence of calcification are to be emphasized in view of the massive pulmonary and mediastinal involvement the patient had, but are typical of sarcoid in its ability to regress. The absence of tubercle bacilli in the lesions is another common feature. The lack of skin and bone lesions is not infrequent; only 25 per cent of the reported cases have had bone involvement and approximately 35 per cent have had skin lesions.

The slowly progressing and relatively asymptomatic course in a young negro showing the extensive pulmonary involvement exhibited roentgenologically early in the disease is striking but not uncommon in sarcoid. The anergy to tuberculin, which was seen initially, is also characteristic. Several months thereafter two nodes broke down, discharging caseous material which on culture was positive for tubercle bacilli. A positive tuberculin reaction was observed later. The nodes apparently went on to heal subsequently. Although this progression to caseous tuberculosis is more often a terminal affair and thus unusual here, the

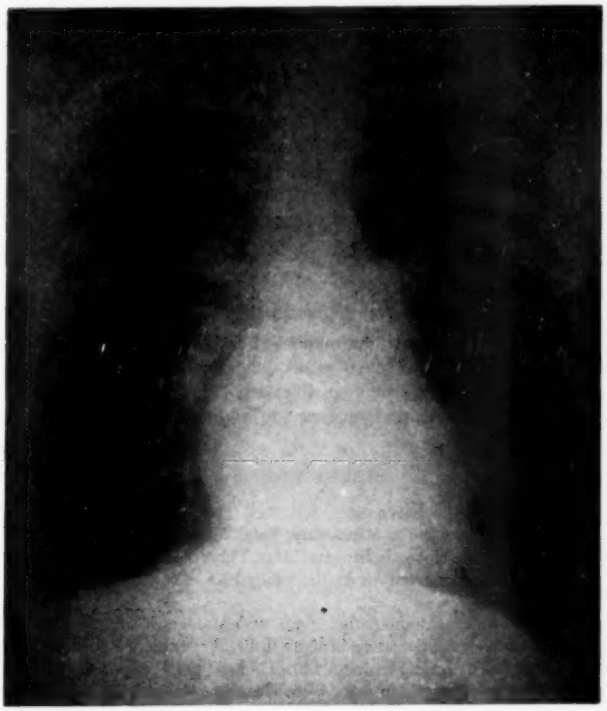

FIG. 7. Chest film taken at Goldwater Memorial Hospital 10 years after the onset of patient's illness, demonstrating the progression to severe emphysema and cor pulmonale.

change in tuberculin reaction has been noted previously by other observers; namely, when active tuberculosis develops in sarcoidosis, the anergy to tuberculin disappears and sensitivity is apparent. All these considerations might suggest that the tubercle organism was responsible for both the tuberculous and the sarcoid types of tissue reaction. In accordance with this concept, the progression from a non-caseating lesion to a caseating one might well be interpreted as due to a decrease in the resistance of the host or an increase in the virulence of the

organism. This, of course, is speculation. One must admit, as Pinner [3] does, that the evidence connecting sarcoid with tuberculosis is purely circumstantial.

The severe pulmonary emphysema and cor pulmonale seen here are unusual in association with Boeck's sarcoid. Schaumann [4] reported one such case in 1933. There are very few others in the literature but the emphysema reported by these authors does not appear to have been nearly as extensive as occurred in this patient. Furthermore, the pulmonary fibrosis described has usually been more severe. The pulmonary hypertension and enlargement of the right heart one can assume to be due to the obliteration of the capillary bed by the emphysema. However, it is more difficult to account for the etiology of the emphysema. The most logical explanation is impingement upon the terminal bronchioles by the granulomatous nodules, causing stenosis of the lumina and resultant emphysema.

From a roentgenological point of view, the changes (figures 4, 5, 6, 7) seen over the 10 year period are impressive. Aside from the development of emphysema, the regression of the initial pulmonary involvement to what was apparently roentgenological normality is worthy of note. The sarcoid lesions, diffuse as they were, were not visible on the roentgen film of the chest taken at the time of the last hospital admission. The lesions, to be sure, were microscopic in size. Nevertheless, the implication is obvious: in the healing of sarcoid, roentgenological normality may develop, yet extensive lesions, although microscopic in magnitude, may still remain.

Summary

A case of miliary sarcoidosis, complicated by caseous tuberculosis, showing the development over a period of 10 years, is presented. The case suggests an etiologic relationship between the two diseases. Severe pulmonary emphysema and resultant cor pulmonale that ensued are additional unusual features rarely seen with Boeck's sarcoid.

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EDITORIAL

AUREOMYCIN

Of the new antibiotics isolated in the attempts to supplement the deficiencies of penicillin and streptomycin, aureomycin at present seems to be the most promising. This substance was first obtained by Duggar and his associates in the Lederle Laboratories from cultures of *Streptomyces aureofaciens*. Extensive laboratory studies as well as some preliminary clinical trials of the drug were reported before the Section on Biology of the New York Academy of Sciences, July 21, 1948.[1]

Aureomycin forms a hydrochloride salt which is stable in dry form and relatively so in simple aqueous solutions which are acid and quite irritating on parenteral injection. It deteriorates rapidly in dilute alkaline solutions such as the usual culture media. It is readily absorbed from the gastrointestinal tract, and effective concentrations in the blood are easily obtained after oral administration. It is excreted rapidly in the urine, maximally from the fourth to the eighth hour, in which it reaches high concentrations.

Aureomycin is relatively nontoxic. Experimental animals survived intravenous injections of 50 mg. per kg., and mice usually survived 2 to 3 gm. per kg. given subcutaneously. Full therapeutic doses, administered orally, often cause some nausea and vomiting or mild diarrhea. This is often relieved by aluminum hydroxide preparations, usually subsides after a few days and rarely necessitates interruption of treatment. If necessary supplementary parenteral injections of aureomycin in procaine solution may be given, although these are painful and may cause more or less troublesome local reactions. Thus far more serious toxic reactions have been rarely if ever encountered.

Preliminary experiments with aureomycin in vitro indicated that it inhibits growth and in much higher concentrations is bactericidal for a large number of pathogenic microörganisms, including both Gram-positive and Gram-negative species. These included hemolytic streptococci, some strains of *Streptococcus faecalis* and other types of nonhemolyzing streptococci, pneumococci, meningococci, gonococci, staphylococci, colon bacilli, typhoid bacilli and other Salmonella, Brucella, Klebsiella and influenza bacilli. Proteus and *Pseudomonas aeruginosa*, however, were relatively resistant. Technical difficulties were encountered in these experiments as well as in titrations of aureomycin in the blood because the drug deteriorates very rapidly in dilute alkaline solutions. The presence of serum lessens its inhibitory action in vitro.

[1] Duggar, B. M., et al.: Aureomycin—a new antibiotic, Ann. New York Acad. Sci., 1948, li, 175–342.

These results, in general, have been confirmed by animal experiments. Thus Bryer et al.[2] found that aureomycin protected mice experimentally infected with hemolytic streptococci, pneumococci Type I, and *Klebsiella pneumoniae*. In general, on a weight for weight basis, its effect approached but did not equal that of penicillin and streptomycin on organisms which were sensitive to the latter antibiotics. Protection from infections with Gram-negative bacilli has been reported, e.g., by Price et al.[3] (typhoid bacilli and colon bacilli), by Little,[4] (typhoid bacilli, *Pasteurella multocida* and *Shigella gallinarum* in chicks), by Spink et al.[5] (Brucella) and by Woodward et al.[6] (tularemia).

The number of patients with such infections thus far reported who have been treated with aureomycin is still relatively small. Finland et al.[7] treated 66 cases of gonococcal urethritis with good results in 49 cases. It was not as effective as penicillin in this series. In four cases of pneumococcal pneumonia and one of acute meningococcemia the results were excellent and comparable to those of penicillin or the sulfonamides.

In a small number of cases of typhoid fever and infections with other Salmonella, the clinical results were less convincing but apparently favorable in several cases.[2, 8]

In infections of the urinary tract favorable results were obtained in many cases, apparently quite equal to those of penicillin and streptomycin.[2, 8] These included cases of infection with colon bacilli as well as cocci, including strains of *Streptococcus faecalis* that were resistant to penicillin. Infections with Proteus and *Pseudomonas aeruginosa* appear usually to be resistant.

Woodward et al.[6] have studied the effects of aureomycin in tularemia. In animal experiments aureomycin exerted greater protective power than either streptomycin or chloromycetin. Three patients, one with a severe infection and in critical condition, recovered promptly, the temperature reaching normal in 36 to 72 hours. They regarded the response as fully equal to that to streptomycin.

The initial results in the treatment of acute brucellosis have been excellent. Bryer et al.[2] reported the successful treatment of one case and subsequently[9] of five cases, all proved bacteriologically (four *B. suis* and one

[2] Bryer, M. S., et al.: Aureomycin, Jr. Am. Med. Assoc., 1948, cxxxviii, 117–119.
[3] Price, C. W., et al.: Bacteriological studies of aureomycin, Ann. New York Acad. Sci., 1948, li, 211–217.
[4] Little, P. A.: Use of aureomycin on some experimental infections in animals, Ann. New York Acad. Sci., 1948, li, 246–253.
[5] Spink, W. W., et al.: Aureomycin therapy in human brucellosis, Jr. Am. Med. Assoc., 1948, cxxxviii, 1145–1148.
[6] Woodward, T. E., et al.: Aureomycin in the treatment of tularemia, Jr. Am. Med. Assoc., 1949, cxxxix, 830–832.
[7] Finland, M., et al.: Aureomycin, a new antibiotic, Jr. Am. Med. Assoc., 1948, cxxxviii, 946–949.
[8] Collins, H. S., et al.: Aureomycin—A new antibiotic: evaluation of its effects in typhoid fever, severe Salmonella infections, and in a case of colon bacillus bacteremia, Ann. Int. Med., 1948, xxix, 1077–1092.
[9] Bryer, M. S., et al.: The treatment of acute brucellosis with aureomycin, Bull. Johns Hopkins Hosp., 1949, lxxxiv, 444–460.

B. abortus). The temperature fell to normal within two to three days, symptoms subsided in four to seven days, and the patients remained well during a period of observation of two to 10 months.

Even more impressive results have been reported by Spink et al.[5] in 24 cases of acute infection with *Brucella melitensis* in Mexico (bacteriologically proved). All were acutely ill and febrile, and several were in critical condition. "Prompt improvement" occurred in every patient treated orally with aureomycin. The temperature fell to normal within two to seven (usually three to four) days, and subsequent cultures were negative. (In an addendum they state that in three cases relapses occurred within one to three months, and larger doses of aureomycin(4 to 6 gm. instead of 2 gm. per day) were suggested.) These results were far superior to those previously observed with streptomycin and sulfadiazine, although streptomycin had been more effective than aureomycin in experiments in vitro and in infected chick embryos.

Perhaps the most important property of aureomycin is its capacity to combat rickettsial infections. Wong and Cox [10] demonstrated marked protective and curative power in embryonated hen's eggs and in animals experimentally infected with strains of rickettsiae from murine and epidemic typhus fever, Rocky Mountain spotted fever, scrub typhus, Q fever and rickettsial pox. Their findings were confirmed by Anigstein et al.[11] in the case of epidemic typhus and spotted fever.

Favorable results have also been reported in cases of rickettsial infections in man. Lennette et al.[12] reported prompt (two to three days) improvement and fall in temperature in 14 of 15 cases of Q fever, all acute and selected because of their relatively advanced age or the severity of the infection. Two patients who relapsed, possibly because treatment was stopped prematurely, responded to a second course.

Ross et al.[13] have reported excellent results in the treatment with aureomycin of Rocky Mountain spotted fever in the Eastern states. Thirteen acute cases confirmed by serological tests, of which seven were severe, all recovered. The temperature fell by crisis, reaching normal after an average interval of two and one-third days. There was a corresponding improvement in the clinical symptoms, and the rash disappeared quickly in those cases whose treatment had been started early. The results were much superior to those previously observed with para-aminobenzoic acid. Schoen-

[10] Wong, S. C., and Cox, H. R.: Action of aureomycin against experimental rickettsial and viral infections, Ann. New York Acad. Sci., 1948, li, 290–305.

[11] Anigstein, L., et al.: Aureomycin. A new antibiotic with antirickettsial properties: Its effect on experimental spotted fever and epidemic typhus, Ann. New York Acad. Sci., 1948, li, 306–317.

[12] Lennette, E. H., et al.: Treatment of Q fever in man with aureomycin, Ann. New York Acad. Sci., 1948, li, 331–342.

[13] Ross, S., et al.: Aureomycin therapy of Rocky Mountain spotted fever, Jr. Am. Med. Assoc., 1948, cxxxviii, 1213–1216.

bach [14] has also reported prompt recovery in one case of Brill's disease (recurrent epidemic typhus) observed in Baltimore.

Viral diseases of the psittacosis group are also susceptible to aureomycin. Wong and Cox [10] reported that aureomycin protected mice from infection with the viruses of psittacosis and of lymphogranuloma venereum, even when the inoculation was intracerebral and treatment was delayed until 72 hours after inoculation. Wright et al.[15] reported favorable results in the treatment of 35 human cases of lymphogranuloma venereum. Buboes diminished in size within four days, rectal bleeding ceased and ulcerations healed, elementary bodies when present disappeared from the lesions, and there was marked general improvement. There was little change, however, in the caliber of the rectal strictures, although the associated symptoms were largely relieved and there was some increase in the caliber of the stools. They also obtained excellent results in three cases of granuloma inguinale (caused by an organism which is usually classed as a bacterium).

Braley and Sanders [16] have reported prompt improvement in five cases of inclusion conjunctivitis and one case of trachoma, both diseases caused by viruses of the psittacosis group.

Aureomycin was not effective in experimental infection with several unrelated viruses, including influenza B and one strain of poliomyelitis.[10]

Favorable results with aureomycin have also been reported in cases of primary atypical (virus) pneumonia. Schoenbach and Bryer [17] reported a series of 16 acute cases, 12 "severely ill," and all with roentgenological evidence of pulmonary lesions. All patients became afebrile within 12 to 72 hours, usually within 24 hours, clinical symptoms improved promptly, and convalescence was uneventful and without relapses. Ten patients had previously received penicillin (seven with sulfadiazine also) without improvement. Finland et al.[18] obtained similar results in 20 cases, all of whom subsequently showed cold agglutinins in the blood. Meiklejohn et al.[19] treated 22 cases of primary atypical pneumonia with aureomycin and a parallel series of 20 cases with penicillin as a control. All of the patients receiving aureomycin showed prompt improvement, similar to that described above. Three suffered a relapse but recovered promptly and permanently when aureomycin was resumed. A third of the control series also recovered promptly, but in

[14] Schoenbach, E. B.: Aureomycin therapy of typhus, Jr. Am. Med. Assoc., 1949, cxxxix, 450–452.

[15] Wright, L. T., et al.: Aureomycin, Jr. Am. Med. Assoc., 1948, cxxxviii, 408–412.
Ibid: The treatment of lymphogranuloma venereum and granuloma inguinale in humans with aureomycin, Ann. New York Acad. Sci., 1948, li, 318–330.

[16] Braley, A. E., and Sanders, M.: Aureomycin in ocular infections, Ann. New York Acad. Sci., 1948, li, 280–289.

[17] Schoenbach, E. B., and Bryer, M. S.: Treatment of atypical pneumonia with aureomycin, Jr. Am. Med. Assoc., 1949, cxxxix, 275–280.

[18] Finland, M., et al.: Aureomycin in the treatment of primary atypical pneumonia, New England Jr. Med., 1949, ccxl, 241–246.

[19] Meiklejohn, G., et al.: Aureomycin in primary atypical pneumonia, Jr. Am. Med. Assoc., 1949, cxl, 391–396.

the others the course was more protracted, and four who became alarmingly ill recovered promptly when aureomycin was administered.

All these reports stress the difficulty in evaluating treatment of a disease with a low mortality, in which early recovery often occurs spontaneously. The results observed in some other clinics have not been as favorable, and more extensive study is required to establish the value of aureomycin in this disease.

That aureomycin may also be useful in the treatment of amebiasis is suggested by the recent report of McVay et al.[20] They administered the drug to 14 patients with "successful" results. In three cases reported in some detail, the symptoms subsided and amebae were no longer demonstrable after the oral administration of 7 to 15 gm. over a period of three to six days. No relapses occurred during a relatively short period of observation.

Although the published evidence does not warrant a final conclusion as to the effectiveness of aureomycin in any of these diseases, it is obvious that the drug is of great practical value. Its activity extends over a far wider range of organisms than that of any antibiotic previously known. Its action on the rickettsiae and the psittacosis group of viruses is of great theoretical interest in that it is the first therapeutic agent which can penetrate the barrier of the cell membrane and effectively attack infectious agents which are ensconced within the tissue cells. Its apparent failure to affect other viruses may be disappointing but is not surprising. The psittacosis viruses differ in many respects from the other viruses, and they seem in many ways more closely related to the rickettsiae and the "simpler" bacteria.

From the standpoint of administration, aureomycin offers many obvious advantages. It is highly effective when given orally. Thus far no serious toxic effects have been described, although gastrointestinal disturbances may be troublesome, especially if full doses (3 to 6 gm. per day) are required. Eventually evidences of toxic action and of sensitization may be anticipated, but it seems probable that these will be rare. Thus far there has been little if any tendency for susceptible organisms to become resistant. Experiments designed to accomplish this have resulted in only a relatively trivial increase in resistance as a rule, in sharp contrast to streptomycin. Until the present cost (at retail about four dollars a gram) is reduced, however, it is not likely to replace penicillin in the treatment of infections which are susceptible to the latter.

At present aureomycin is the treatment of choice if not the only effective measure in lymphogranuloma venereum, granuloma inguinale, in all rickettsial infections, in acute brucellosis, probably in primary atypical pneumonia and possibly in typhoid fever and other Salmonella infections, although the evidence of its effectiveness here is much less convincing. Aureomycin

[20] McVay, L. V., et al.: A preliminary report of the successful treatment of amebiasis with aureomycin, Science, 1949, cix, 590–591.

promises to be valuable as a substitute for streptomycin in infections with other Gram-negative bacilli, such as Klebsiella, Hemophilus and in tularemia, in which streptomycin-resistant strains have developed or in patients who show evidence of toxic injury from streptomycin.

The same is probably true of the usual coccal infections which are routinely treated with penicillin. Aureomycin has been used successfully, e.g., in certain cases of infection with penicillin-resistant strains of Staphylococcus, *Streptococcus faecalis* and *S. viridans* (in bacterial endocarditis). There is as yet no evidence that aureomycin would be superior to penicillin in most cases of such infections. Because of its wide range of activity, however, a strong tendency may be anticipated to administer aureomycin blindly to many patients with infections in which it is difficult or inconvenient to make a precise bacteriological diagnosis.

The relative value of chloromycetin and other new antibiotics can not be assessed at present. Chloromycetin is evidently more effective than aureomycin in typhoid fever. Undoubtedly the introduction of aureomycin marks an important advance in the treatment of infectious diseases.

P. W. C.

REVIEWS

The Hormones: Physiology, Chemistry and Applications. Volume I. Edited by GREGORY PINCUS and KENNETH V. THIMANN. 886 pages; 15.5 × 23.5 cm. Academic Press, New York. 1948. Price, $13.50.

Those physicians who are curious about the procedures involved in extracting, synthesizing, assaying and otherwise preparing the glandular products which bulk so large in their daily practice will find their answers here, but only if their training in chemistry and physics was thorough and their memories are long. Written primarily for the specialist and research worker in the endocrine field, this book is not easy reading. The list of authors is distinguished and they speak with authority commensurate with their eminence. Matters of immediate clinical interest are dealt with sparingly, if at all, and the concern is almost exclusively with the more subtle refinements of chemical technics. A second volume is to follow in due course and here the more clinical aspects of endocrinology will receive more thorough consideration.

To summarize briefly, roughly three-fourths of the contents of the book are devoted to the hormones of the gastrointestinal tract, the parathyroids, gonads, adrenal cortex and the anterior pituitary, and the remaining one-fourth to an excellent discussion of hormones in plants and in the insects and crustaceans. Omitted, however, are the hormones of the adrenal medulla, posterior pituitary and thyroid. The latter deficiencies are to be corrected in the second volume.

The most grievous fault of the book is a lack of balance between the various chapters. Such flaws are not uncommon in collaborative efforts of this sort and perhaps a nice distribution of emphasis cannot be achieved under the circumstances. However, a little closer editorial supervision might have helped. For instance, the chapter on the androgens gives an excellent and exhaustive account of the excretion levels of these compounds in humans of all ages, sexes and physical condition. A proper eye for the niceties of proportion might lead one to expect a similar discussion in the chapter on the estrogens. Instead we find that the excretion levels of these compounds are not even mentioned. Another singular omission concerns luteotrophin, which is not discussed in the text although the word does appear in the index under prolactin.

On the whole the chapters on hormones in plants, insects, crustaceans, the gastrointestinal tract, the parathyroid gland and the pancreas are broadly treated and quite inclusive. The chapter on the hormones of the anterior lobe contains excellent accounts of how these elusive compounds are separated, purified and assayed, together with their physico-chemical properties. Treatment of the gonadal hormones is almost entirely chemical, as is that of the hormones of the adrenal cortex. In the latter case 50 of the 60 pages devoted to this gland are given over to a discussion of the chemistry of the cortical steroids and the remaining ten pages to a consideration of the metabolism of the gland.

Up to this point each gland of internal secretion has been dealt with as a separate anatomical entity and each hormone considered more or less by itself. In the last two chapters, however, concerning lactation the pace suddenly shifts and now, instead of discussing extraction technics and their ancillary problems, the reader is asked to consider a process with endocrinological overtones. There is no objection to this treatment, except that it is not made clear why lactation should be so singled out while other equally important matters, such as electrolyte balance, are not.

Anyone who reads this book, or even glances through it casually, cannot but be impressed by the wealth of material which has poured from the endocrinology laboratories in the last fifty years. From a discipline concerned with cataloguing the more bizarre and less respectable ailments afflicting mankind, it has grown into a unifying

and integrating science which penetrates into every branch of biology. The various bibliographies in the book contain over 3600 titles, only a fraction of the total literature of the field, but quite adequate for the purpose. The index, however, contains less than 4000 entries and this does not seem enough. A recent book, covering much the same field in about the same space, had over 10,000 entries. To cite one omission, the term luteinizing hormone is not even mentioned in the index, nor is its familiar abbreviation LH, even though in the heading of the chapter on interstitial cell stimulating hormone the alternative term LH is given in parentheses and the initials ICSH appear in the index.

As expressed by the editors, the announced purpose of the book is to "make a contribution to the orderly assemblage of knowledge essential to scholarship." Considered broadly this goal is attained and in a field that is filled with bewildering complexities. We hope that the appearance of the second volume of the series is not too long delayed.

DIETRICH C. SMITH

Case Studies in the Psychopathology of Crime. Volumes III and IV. By BEN KARPMAN, M.D., Senior Medical Officer and Psychotherapist, St. Elizabeth's Hospital, Washington, D. C. 834 and 875 pages; 21.5 × 27.5 cm. Boxed. Medical Science Press, Washington, D. C. 1948. Price, $28.00.

Ben Karpman has again contributed two massive volumes to his monumental work on the psychopathology of crime, and has further emphasized that of all social problems, crime is undoubtedly the most pressing, and certainly the most demoralizing. As he points out in his introduction, "most economic expression of the cost of crime, however high, can never depict its profound and far-reaching effect on the community." These case studies by Ben Karpman very clearly bring out that, through an intensive study of the lives of individual criminals, the uncovering of the psychogenic factors very definitely gives us an understanding of the fundamental drives which lead people into lives of criminal behavior.

In these two volumes a detailed report is given on eight cases, ten cases having been reported in the previous volumes. Of these eight cases, all were involved in murders, two of them also involving robbery. A psychoanalytic approach is used in each case, and much treatment material is recorded. There was no attempt made in these studies to show that criminality is due to purely psychogenic and emotional influences. It is evident that Dr. Karpman, the psychiatrist, like any physician, treated the "criminal" as a patient, an individual who was psychically sick, and whose symptoms were expressed in antisocial behavior. He not only studied each patient for the factual material that he could obtain, but he also tried to give the patient insight.

The author has been criticized in the past for the length of his case studies, and it is evident from these volumes that he has exhausted all his material. This, of itself, makes these works of inestimable value. He took the material as it came from the patient and laid no more emphasis on one aspect than on another, but tried to stress the all-around emotional aspects of the personality. Since sex behavior is an important part of everybody's life, necessarily in these cases, there were some rather glaring examples of sexual activity, both normal and abnormal.

In reviewing these two books, it is impossible to show adequately the painstaking work that was involved in the preparation of the material. Anyone who wishes to get a clear understanding of the psychogenic factors which go in to make up so-called criminal behavior will not find a better source than in this series of case reports, which also clearly bring out the technic of an analytic approach to the study of personality. Few people have the patience and the perseverance of Ben Karpman, who, over the years, has persisted in an attempt to interpret these misfits. Most certainly these

case studies are not written for lay consumption and are restricted in sale. Any physician interested in the study of personality will find these case studies a valuable addition to his library. No physician interested in understanding crime can afford to be without these four volumes.

J. L. McC.

Tuberculosis in Childhood. By DOROTHY STOPFORD PRICE, M.D. (univ. Dublin), Physician, St. Ultan's Infant Hospital, Dublin; with a chapter on Tuberculous Orthopaedic Lesions and Other Contributions by HENRY F. MACAULEY, M.Ch., F.R.C.S.I., Orthopaedic Surgeon, Mater Misericordiae Hospital, Dublin. Second edition, fully revised with 87 illustrations. 219 pages; 13 × 19 cm. The Williams and Wilkins Co., Baltimore. 1948. Price, $7.00.

In most monographs one expects to obtain an approach to a particular topic from several points of view. This little book deals didactically with the problem of tuberculosis in children from the standpoint of the clinician without devoting too much attention to fundamental theoretic considerations or to presenting opposing arguments on controversial issues. Such an approach may not be of much use in discovering the truth but it is perhaps helpful to one who seeks a satisfactory working knowledge of childhood tuberculosis. The author draws from her own experiences and case studies to illustrate certain well known features of the disease. Reproductions of roentgenograms are used liberally to illustrate points under discussion; unfortunately some are so poor as to be virtually worthless. The print also is hard to read and the price tag on the book is an eloquent commentary on inflationary trends in present day economy.

A. H.

A Primer of Electrocardiography. Second Edition. By GEORGE E. BURCH, M.D., F.A.C.P., Henderson Professor of Medicine, Tulane University, etc., and TRAVIS WINSOR, M.D., F.A.C.P., Assistant Clinical Professor of Medicine, University of Southern California Medical School, etc. 245 pages; 15 × 23.5 cm. Lea and Febiger, Philadelphia, Pennsylvania. 1949. Price, $4.50.

The emphasis in the teaching of electrocardiography is properly shifting from the memorization of certain electrical patterns to the development of an understanding of the basic physiological mechanisms which are reflected in those electrical changes which are recorded as the electrocardiogram. This concise text is an eloquent expression of the newer point of view. It stresses mechanisms rather than patterns, and in so doing provides an excellent basis for the understanding of electrocardiography. The illustrations are more numerous than in the first edition, and continue highly diagrammatic and exceedingly useful. In accordance with current trends, unipolar leads have replaced bipolar leads of the first edition.

This is probably the text best suited to both students and clinicians as an introduction to this rapidly growing field. While brevity and idealized illustrations are helpful in such a text, actual electrocardiograms and serial records are indispensable in training one to make the most of this useful laboratory method. It is therefore hoped that some day there will be available an atlas organized in the same fashion.

S. S.

Modern Trends in Psychological Medicine. Edited by NOEL G. HARRIS, M.D., F.A.C.P., F.R.C.P., D.P.M. 450 pages; 17.5 × 25 cm. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. 1948. Price, $10.00.

This volume contains 19 chapters written largely by British authors. Two chapters are by Americans, one on Psychotherapy by Dr. John C. Whitehorn, and one on Psychological Medicine and World Affairs by Dr. Jules H. Masserman. The volume covers a wide range of topics related to psychiatry and medicine, and on the whole the subjects are presented in a very readable style, with useful bibliographies covering each topic. As might be expected, especial emphasis is placed on the work of British investigators and, as a result, a great deal of valuable work by American authors on psychosomatic problems is omitted. There is similarly a neglect of the distinctive contributions to this field made by American psychoanalysts. This volume will be of particular interest to those who wish to acquaint themselves with recent British investigations in the field of psychological medicine.

H. W. N.

Cardiology. By WILLIAM EVANS, M.D., D.Sc., F.R.C.P., Physician to the Cardiac Department of the London Hospital. 330 pages; 17 × 24.5 cm. Paul B. Hoeber, Inc., New York. 1948. Price, $7.50.

This book is "meant to serve the need of the medical student who seeks a more concise treatise on this subject in preparation for a higher or qualifying examination." The text contains something about most cardiac diseases and conditions. The sections on physical diagnosis and phonocardiography are generally more complete than are the clinical descriptions, which often seem too sketchy. Acute rheumatic fever, Friedreich's disease, and myotonia atrophica are covered in two pages each. The roentgen-rays are excellent in selection and reproduction. The discussion of electrocardiography is quite inadequate. Electrocardiographic illustrations are chiefly limited to three limb leads, plus an occasional CR lead. The author recommends CR-1, CR-4, and CR-7, if the limb lead electrocardiogram is in doubt.

Evans believes "percussion as a means of detecting the size of the heart may be discarded as obsolete." He advises that the term "mitral incompetence" be discarded. "Mitral stenosis (is) a comprehensive disease and not solely . . . a condition producing a gradual closing effect of the mitral valve. Whenever a systolic murmur in the mitral area is regarded as evidence of mitral disease, it should be referred to as mitral stenosis and not as incompetence." The author uses the term auricular flutter and paroxysmal auricular tachycardia interchangeably, because of "the common incidence of A-V dissociation" shown in CR-1 in these patients. This is interesting in view of Prinzmetal's recent work tending to disprove circus movement in auricular flutter and auricular fibrillation. This book contains no bibliography.

This text may be suitable for preparing for certain examinations; but it would seem to fall short of being equal to some of the good texts available to medical students seeking information concerning cardiac conditions.

S. S.

BOOKS RECEIVED

Books received during May are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

The Adrenal Gland. By FRANK A. HARTMAN, Ph.D., Research Professor of Physiology, The Ohio State University, and KATHARINE A. BROWNELL, Ph.D., Instructor in Physiology, The Ohio State University. 581 pages; 24 × 15.5 cm. 1949. Lea & Febiger, Philadelphia. Price, $12.00.

An Atlas of Electrocardiography. By WILLIAM DRESSLER, M.D., Cardiologist, Maimonides Hospital in Brooklyn, etc.; and HUGO ROESLER, M.D., F.A.C.P., Cardiologist, Department of Medicine, Associate Professor of Radiology, Temple University Medical School and Hospital, Philadelphia. 503 pages; 21 × 27.5 cm. 1949. Charles C. Thomas, Publisher, Springfield, Illinois. Price, $14.00.

Clinical Auscultation of the Heart. By SAMUEL A. LEVINE, M.D., Clinical Professor of Medicine, Harvard Medical School, etc.; and W. PROCTOR HARVEY, M.D., Research Fellow in Medicine, Harvard Medical School, etc. 327 pages; 24 × 15.5 cm. 1949. W. B. Saunders Company, Philadelphia. Price, $6.50.

The Common Form of Joint Dysfunction: Its Incidence and Treatment. By WILLIAM KAUFMAN, Ph.D., M.D. 208 pages; 27 × 17.5 cm. 1949. E. I. Hildreth & Company, Brattleboro, Vermont. Price, $8.75, including postage.

Food and Facts for the Diabetic. By JOSEPH H. BARACH, M.D., F.A.C.P., Associate Professor of Medicine, School of Medicine, University of Pittsburgh. 113 pages; 24.5 × 16 cm. 1949. Oxford University Press, New York. Price, $4.00.

Fundamentals of Internal Medicine. 3d Ed. By WALLACE MASON YATER, A.B., M.D., M.S. (in Med.), F.A.C.P., Director, Yater Clinic, Washington, D. C., etc. 1451 pages; 25.5 × 17 cm. 1949. Appleton-Century-Crofts, Inc., New York. Price, $12.00.

How to Become a Doctor: A Complete Guide to the Study of Medicine, Dentistry, Pharmacy, Veterinarian Medicine, Occupational Therapy, Chiropody and Foot Surgery, Optometry, Hospital Administration, Medical Illustration, and the Sciences. By GEORGE R. MOON, A.B., M.A., Examiner and Recorder, University of Illinois Colleges of Medicine, Dentistry and Pharmacy. 131 pages; 22.5 × 14.5 cm. 1949. The Blakiston Company, Philadelphia. Price, $2.00.

Living Wisely and Well: A Discussion of Techniques of Personal Adjustment. By WILLIAM B. TERHUNE, M.D., Editor, DOUGLAS A. THOM, M.D., KENNETH E. APPEL, M.D., and WINFRED OVERHOLSER, M.D., Sc.D. With a Foreword by DR. EDWIN G. ZABRISKIE, Professor Emeritus of Clinical Neurology, College of Physicians and Surgeons, Columbia University. 95 pages; 21 × 14 cm. 1949. E. P. Dutton & Company, Inc., New York. Price, $2.00.

Malignant Disease and Its Treatment by Radium. Volume II, Second Edition. By SIR STANFORD CADE, K.B.E., C.B., F.R.C.S., M.R.C.P., Surgeon, Westminster Hospital, etc. With a Foreword by SIR ERNEST ROCK CARLING, F.R.C.P., F.R.C.S., F.F.R., Consulting Surgeon and Vice-President, Westminster Hospital. 430 pages; 23.5 × 15 cm. 1949. The Williams & Wilkins Company, Baltimore. Price, $12.50.

Mycoses and Practical Mycology: A Handbook for Students and Practitioners. By N. GOHAR, M.R.C.S., (Eng.), L.R.C.P. (Lond.), Assistant Professor of Parasitology and Mycology, Department of Clinical Pathology, Kasr el Ainy Faculty of Medicine, Fouad I University, Cairo, Egypt; with a Foreword by SIR PHILIP MANSON-BAHR, C.M.G., D.S.O., M.A., M.D., D.T.M. & H. (Cantab.), F.R.C.P. (Lond.). 234 pages; 22 × 14 cm. 1948. The Williams & Wilkins Company, Baltimore. Price, $6.00.

Nutrition and Diet in Health and Disease. 5th Ed. By JAMES S. MCLESTER, M.D., Professor of Medicine, University of Alabama, Birmingham. 800 pages; 24 × 16 cm. 1949. W. B. Saunders Company, Philadelphia. Price, $9.00.

Obesity. By EDWARD H. RYNEARSON, M.D., F.A.C.P., Division of Medicine, Mayo Clinic, etc., and CLIFFORD F. GASTINEAU, M.D., Fellow in Medicine, Mayo Foundation. 134 pages; 22.5 × 14.5 cm. 1949. Charles C. Thomas, Publisher, Springfield, Illinois. Price, $3.50.

Poliomyelitis: Papers and Discussions Presented at the First International Poliomyelitis Conference. Compiled and Edited for the INTERNATIONAL POLIOMYELITIS CONGRESS. 360 pages; 26 × 18 cm. 1949. J. B. Lippincott Company, Philadelphia. Price, $5.00.

Syphilis: Its Course and Management. By EVAN W. THOMAS, M.D., Professor of Clinical Medicine, New York University College of Medicine, etc. Foreword by JOHN F. MAHONEY, M.D., Director of Venereal Disease Research Laboratory, United States Public Health Service. Chapter on "Public Health Aspects of Syphilis" by THEODORE J. BAUER, M.D., Chief, Venereal Disease Division, United States Public Health Service. 317 pages; 24 × 16 cm. 1949. The Macmillan Company, New York. Price, $5.50.

Textbook of Medicine. 9th Ed. By Various Authors. Edited by SIR JOHN CONYBEARE, K.B.E., M.C., D.M. (Oxon.), F.R.C.P., Physician to Guy's Hospital, London. 875 pages; 24.5 × 17 cm. 1949. The Williams & Wilkins Company, Baltimore. Price, $8.00.

COLLEGE NEWS NOTES

A.C.P. Autumn of 1949 Schedule of Postgraduate Courses

The following group of courses has been arranged through the generous co-operation of the Directors and Institutions at which the courses will be given. Where facilities are available these courses will be open to non-members with adequate preliminary training. However, registrations from non-members of the College may not be accepted more than three weeks in advance of the opening of any course. An effort will also be made to accommodate foreign physicians visiting this country.

The courses are made available by the College to its members at a minimum cost because the College assumes responsibility for promotion, advertising and registration. Obviously, a portion of the cost of the courses comes from dues paid by members; therefore, it is appropriate that non-members, when admitted, shall pay an increased fee. Specified fees are $30.00 per week to members of the College; $60.00 per week to non-members, except physicians taking the course under the auspices of Public Law 346 (G.I. Bill of Rights), to whom the $30.00 per week rate applies.

All registrations must be made through the Executive Offices of the College, 4200 Pine Street, Philadelphia 4, Pa.

No. 1—CARDIOLOGY. National Institute of Cardiology of Mexico, Mexico, D. F.; Ignacio Chavez, M.D., F.A.C.P., Director; August 15–26, 1949. A.C.P. Members, $60.00; Non-members, $120.00.

This is a repetition of a course given most successfully during the Summer of 1948. It is unique in that it offers a combined vacation and period of postgraduate study. Classes will meet from 9 a.m. to 1 p.m. daily and each afternoon and the intervening week-end will be available for tours, inspection trips and entertainment. Alternate periods of the day are devoted to didactic teaching and clinical teaching in the wards and laboratories. The faculty consists of outstanding authorities in Mexico, all of whom speak English, with two distinguished teachers from the United States, Dr. George Morris Piersol, Secretary-General of the American College of Physicians; Professor of Medicine and Chairman of the Department of Medicine and Director of the Center for Instruction and Research in Physical Medicine, University of Pennsylvania Graduate School of Medicine; and Dr. William Dock, Professor of Medicine of the Long Island College of Medicine, Brooklyn, N. Y. Those who took the course in 1948 expressed amazement at the strides that have been made in this field in Mexico and sent to the College most enthusiastic reports on the quality of the course.

Mexico is at such an elevation that the climate is delightfully cool even in the midst of summer. There is so much of interest and attraction that the vacation features alone should attract a large registration. Accommodations are available for wives and members of the family.

A full and detailed bulletin of the course and data concerning directions for entry into Mexico, money exchange and hotel accommodations is available on request to the Executive Secretary of the College. It is extremely important that registrations be filed without delay.

No. 2—GASTRO-ENTEROLOGY. University of Chicago School of Medicine, Chicago, Ill.; Walter L. Palmer, M.D., F.A.C.P., Director; one week, October 10–14, 1949. A.C.P. Members $30.00; Non-members, $60.00.

This course has been given on several previous occasions and is truly one of the great courses on the College schedule.

No. 3—CLINICAL NEUROLOGY. Jefferson Medical College of Philadelphia, Philadelphia, Pa.; Bernard J. Alpers, M.D., F.A.C.P., Director; October 17–21, 1949. A.C.P. Members, $30.00; Non-members, $60.00.

This course is offered for those without special training in Neurology and is directed toward a discussion of the pertinent problems in clinical neurology, illustrated by case material wherever possible. It is organized especially for the internist, and it has been given previously with great satisfaction to the registrants. It is one of the finest courses in a subject closely allied with internal medicine.

No. 4—PRECLINICAL SCIENCE IN INTERNAL MEDICINE. Washington and St. Louis Universities, St. Louis, Mo.; W. Barry Wood, M.D., F.A.C.P., and Ralph A. Kinsella, M.D., F.A.C.P., Directors; October 24–29, 1949. A.C.P. Members, $30.00; Non-members, $60.00.

This is an entirely new course on the College schedule. Part of it will be given at Washington University School of Medicine and part at the St. Louis University School of Medicine.

No. 5—RECENT ADVANCES IN THE DIAGNOSIS AND TREATMENT OF CARDIOVASCULAR DISEASE. Massachusetts General Hospital, Boston, Mass.; Howard B. Sprague, M.D., F.A.C.P., and Edward F. Bland, M.D., Directors; November 14–19, 1949. A.C.P. Members $30.00; Non-members, $60.00.

Heretofore this course has been given annually under the direction of Dr. Paul D. White, ably assisted by Dr. Sprague and others. Because of other commitments, Dr. White is no longer able to organize and direct the course but he will participate in the instruction and assist the Directors. This is one of the most popular courses ever given by the College.

No. 6—BIOLOGICAL AND PHYSIOLOGICAL APPROACHES TO INTERNAL MEDICINE. University of Wisconsin Medical School, Madison, Wis.; William S. Middleton, M.D., F.A.C.P., and Karver L. Puestow, M.D., F.A.C.P., Directors; November 28–December 2, 1949. A.C.P. Members $30.00; Non-members, $60.00.

To a large degree this is a repetition of the very fine course in Internal Medicine organized and directed for the College by Dr. Middleton during the Autumn of 1947. It is to be very comprehensive and inclusive and it will cover the current concepts as they relate to the problems within the field of Internal Medicine.

No. 7—BLOOD DYSCRASIAS. Medical College of Alabama, Birmingham, Ala.; James B. McLester, M.D., F.A.C.P., Director; December 6–10, 1949. A.C.P. Members $30.00; Non-members, $60.00.

This is a new course on the College schedule. It is especially scheduled to meet a demand to furnish advanced instruction in the field of Hematology to physicians in the Southeastern part of the country. Outstanding authorities are being invited from the University of Tennessee, Emory University, Vanderbilt University, Duke University, Tulane University of Louisiana, Harvard Medical School and the Oak Ridge Institute of Nuclear Studies to join the faculty. Advanced instruction will be offered in the form of lectures, case reports and staff conferences in the mornings and laboratory studies in the afternoons. The last day of the course, Saturday, December 10, will be devoted to the Southeastern Regional Meeting of The American College of Physicians comprising Alabama, Florida, Georgia, South Carolina and Cuba.

No. 8—THE PHYSIOLOGICAL APPROACH TO CLINICAL PROBLEMS IN THE CARDIOVASCULAR DISEASES. University of Southern California

School of Medicine, Los Angeles, Calif.; George C. Griffith, M.D., F.A.C.P., Director; December 5–10, 1949. A.C.P. Members $30.00; Non-members, $60.00.

This course has appeared on the College program on several previous occasions and is definitely an outstanding course in Cardiology. The course covers a rapid review of the fundamental basic principles underlying the problems in Cardiology. Recent advances will be emphasized. In addition to the lectures and demonstrations, illustrative case studies will be presented to small groups.

A.C.P. Regional Meetings

The following Regional Meetings are in course of organization and others will be announced in succeeding issues:

Territory	Place of Meeting	Date	Governor and Chairman	Guest Speaker
North Dakota	Grand Forks, N. D.	Sept. 10, 1949	Robert B. Radl, M.D., F.A.C.P., Bismarck, N. D.	George F. Strong, M.D., F.A.C.P., 1st Vice President, Vancouver, B. C.
Montana, Wyoming, Idaho	Great Falls, Mont.	Sept. —, 1949	Harold W. Gregg, M.D., F.A.C.P., Butte, Mont.	
Oklahoma	Oklahoma City, Okla.	Sept. 10, 1949	Wann Langston, M.D., F.A.C.P., Oklahoma City, Okla.	William S. Middleton, M.D., F.A.C.P., President-Elect, Madison, Wis.
Western Pennsylvania	Pittsburgh, Pa.	Sept. 21, 1949	Charles W. Morton, M.D., F.A.C.P., Pittsburgh, Pa.	Reginald Fitz, M.D., F.A.C.P., President, Boston, Mass. (invited)
Western New York	Buffalo, N. Y.	Oct. 1, 1949	Edward C. Reifenstein, M.D., F.A.C.P., Syracuse, N. Y.	Reginald Fitz, M.D., F.A.C.P., President, Boston, Mass. E. R. Loveland, Executive Secretary, Philadelphia, Pa.
Eastern Canada and New England: Maritime Provinces, Quebec, Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont	Montreal, P. Q.	Sept. 23–24, 1949	Arthur T. Henderson, M.D., F.A.C.P., Montreal, Que.	Reginald Fitz, M.D., F.A.C.P., President, Boston, Mass.
MID-WEST: Indiana, Illinois, Michigan, Minnesota, Wisconsin	Indianapolis, Ind.	Nov. 19, 1949	James O. Ritchey, M.D., F.A.C.P., Indianapolis, Ind.	
New Jersey	Newark, N. J.	Nov. 30, 1949	George H. Lathrope, M.D., F.A.C.P., Newark, N. J.	George Morris Piersol, M.D., F.A.C.P., Secretary-General, Philadelphia, Pa. William D. Stroud, M.D., F.A.C.P., Treasurer, Philadelphia, Pa. E. L. Bortz, M.D., F.A.C.P., Regent, Philadelphia, Pa., et al.
SOUTHEASTERN: Alabama, Florida, Georgia, South Carolina, Cuba	Birmingham, Ala.	Dec. 10, 1949	E. Dice Lineberry, M.D., F.A.C.P., Birmingham, Ala.	*
Kansas	Kansas City, Kans.	Mar. 17, 1950	William C. Menninger, M.D., F.A.C.P., Topeka, Kans.	Hugh J. Morgan, M.D., F.A.C.P., Regent, Nashville, Tenn.

* The Regional Meeting will be the concluding feature of a Postgraduate Course in Blood Dyscrasias given at the Medical College of Alabama under the auspices of the American College of Physicians and the directorship of James B. McLester, M.D., F.A.C.P., December 6–9, 1949.

Specific arrangements also are being made for Regional Meetings during the Autumn in Arizona, Eastern Pennsylvania, Virginia, Ohio, Tennessee, North Carolina, Missouri and Texas.

Fellowships for Latin-American Physicians

The American College of Physicians and the W. K. Kellogg Foundation, with the coöperation of the U. S. Department of State and of medical schools in the U. S. A., Canada and Latin-American countries, will shortly inaugurate a program of post-graduate medical fellowships. Outstanding young physicians will be nominated to the College and Foundation by local committees in the countries to the south, and those to whom fellowships are awarded will be brought to this country for a year or more of special training. It is anticipated that the first fellows will begin their studies during the autumn of 1949.

Eligibility requirements include citizenship in the country from which application is made and familiarity with its culture and economy, graduation from an acceptable medical school and completion thereafter of an internship of 12 months or more, ability to use the English language, and assurance of a subsequent teaching affiliation with a medical school in the native country. Those needing some training in English will be assigned to a special course for the purpose in the United States.

Designed to stimulate progress in the teaching of internal medicine and research, and to help the most promising young doctors of medicine in these countries to prepare for teaching and research careers in their native countries, the program also will serve to increase understanding among the American republics by serving as a medium for the exchange of knowledge and acquaintanceships.

The American College of Physicians, operating through its Committee on Fellowships and Awards, will undertake to arrange a suitable program of study in internal medicine or its subspecialties, such as cardiology, gastro-enterology, etc., in widely recognized medical education centers in this country, and to place the fellows appropriately under preceptors in these institutions.

The W. K. Kellogg Foundation will provide each fellow with a monthly stipend adequate for his basic living costs, an allowance for necessary travel within this country or Canada, and will defray the tuition for courses recommended by the preceptor and approved by the sponsors. In view of the pressing need of Latin-American medical libraries, the Foundation will reimburse the fellow for the cost of required textbooks on condition that they become the property of the medical school in which the fellow will teach upon his return home.

Representatives of the Foundation will visit the fellows periodically during their stay in this country for conferences with them and their preceptors, thus to follow their progress. They will also be visited at intervals after their return to their home institutions in an effort to evaluate the end results of their training and to offer any possible assistance to improve teaching, research and practice in the field of internal medicine in their respective countries.

A.C.P. Research Fellowships, 1950–1951

The American College of Physicians announces that a limited number of Research Fellowships in Medicine will be available from July 1, 1950, to June 30, 1951. These Fellowships are designed to provide an opportunity for research training either in the basic medical sciences or in the application of these sciences to clinical investigation. They are for the benefit of physicians who are in the early stages of their preparation for a teaching and investigative career in Internal Medicine. Assurance must be pro-

vided that the applicant will be acceptable in the laboratory or clinic of his choice and that he will be provided with the facilities necessary for the proper pursuit of his work. The stipend will be from $2,200 to $3,200.

Application forms will be supplied on request to The American College of Physicians, 4200 Pine St., Philadelphia 4, Pa., and must be submitted in duplicate not later than October 1, 1949. Announcement of awards will be made November, 1949.

1949 Membership Directory

The work of preparing the biographical data concerning members of the American College of Physicians from the information submitted by members recently on the 1949 Directory Form is well under way, and it is hoped that publication of the Directory will take place in the early Autumn of this year.

The Directory will contain not only a complete list of members, arranged according to their geographical locations, but an alphabetical listing showing office and home addresses, medical school and year of graduation, year of birth, more important current appointments, specialty board certification, and year of election to current College rank, as well as the currently amended Constitution and By-Laws and information concerning A.C.P. Research Fellowships, Awards, Annual Sessions, etc.

The price, postpaid, if ordered in advance of publication will be $4.00 a copy to members of the College; $5.00, to institutions and non-members. The post-publication prices will be increased.

Specialty Board Notices

American Board of Internal Medicine; William E. Werrell, M.D., Asst. Secretary-Treasurer, 1 W. Main St., Madison 3, Wis. (1) From January 1, 1948, only one written examination will be held each year. The examination will be held in various centers in the United States, the location depending on the number of candidates in a given area. (2) All candidates must be active members in good standing in their County and State Medical Societies, in their State of legal residence. Under unusual and exceptional circumstances the Board reserves the privilege of modifying this requirement. (This ruling shall not apply to commissioned officers of the U. S. Army, U. S. Navy, or U. S. Public Health Service who are otherwise members of the American Medical Association.) (3) An additional fee of $10.00 is required for each written reëxamination. An additional fee of $20.00 is required for each oral reexamination. (4) The next written examination will be given October 17, 1949.

American Board of Pathology; Dr. Robert A. Moore, Secretary-Treasurer, 507 Euclid Ave., St. Louis, Mo. Examination at Chicago, October 7–8, 1949; closing date for applications, September 1.

The American Board of Pediatrics, Inc.; John McK. Mitchell, M.D., Executive Secretary, 6 Cushman Rd., Rosemont, Pa. Oral examination, Cleveland, September 16–18, 1949; New York City, October 21–23, 1949; Chicago, December 9–11, 1949.

The American Board of Preventive Medicine and Public Health, Inc.; Ernest L. Stebbins, M.D., Secretary-Treasurer, 615 N. Wolfe St., Baltimore 5, Md. Examinations, New York City, October 22–24, 1949.

American Board of Psychiatry and Neurology, Inc.; F. J. Braceland, M.D., Secretary-Treasurer, 102 2nd Ave., S.W., Rochester, Minn. Special examinations in Neurology, Psychiatry, or Neuropsychiatry, Chicago, October 24–25, 1949. Closing date for receipt of applications for these special examinations, occasioned by the large numbers applying for the regular semi-annual examinations, was July 15, 1949.

Course in Electrocardiography

The annual intensive two-week course in Electrocardiography for *graduate physicians* will be given at Michael Reese Hospital in Chicago, under the personal direction of Dr. Louis N. Katz, Director of Cardiovascular Research, from August 15 to August 27, 1949, inclusive. Group and individual instruction will be given, and the course is open to beginning and advanced students in Electrocardiography. The course will meet daily from 8:00 a.m. to 5:00 p.m. Tuition fee is $150.00.

Further information and a copy of the lecture schedule may be obtained on application to Dr. Samuel Soskin, Dean, Michael Reese Hospital Postgraduate School, Twenty-ninth Street and Ellis Avenue, Chicago 16, Illinois.

University of California Extension Postgraduate Medical Courses

Physics in Radiation Therapy, San Francisco, September 6–9, 1949. This course will be conducted at the University of California Medical Center, with Dr. Robert S. Stone as Chairman. Dr. Edith H. Quimby, Associate Professor of Radiology, Columbia University College of Physicians and Surgeons, will be the guest instructor. The course will consist of 10 lectures of one and one-half hours each, and the subject matter will consist of physics as it pertains to ionizing radiations, whether from x-ray tubes, radium or other radioactive materials. Emphasis will be placed on the basic principles and their application to therapy problems.

Copies of the detailed printed program are available through Stacy R. Mettier, M.D., F.A.C.P., Head of Postgraduate Instruction, Medical Extension, University of California Medical Center, San Francisco 22, Calif.

Clinical Neurology in Medical Practice, Los Angeles, July 25–30, 1949. This course, which will feature recent advances, will be given at the Neuropsychiatric Hospital of the Veterans Administration Center, Los Angeles, under the aegis of the University of California, with a distinguished staff of experts from the medical schools and hospitals of Los Angeles and from the Veterans Administration.

Detailed outlines may be obtained from the Office of Medical Extension, University of California, Los Angeles 24, Calif.

International Society of Internal Medicine

The International Society of Internal Medicine will hold its second meeting in Paris in the spring of 1950. This organization was founded as a result of the efforts of a group of Swedish and Swiss physicians with the approval and assistance of UNESCO. An organization meeting, held in Basle in September, 1948, was attended by physicians from sixteen countries. Many of the founders' group (nearly all of whom are teachers of medicine in their respective countries) have travelled or studied in the United States. The organization is a member of the Association of International Medical Congresses, which met under the auspices of WHO and UNESCO in Brussels in April, 1949.

The purpose of the International Society of Internal Medicine, as stated in its constitution, is "to contribute to the development of scientific knowledge and education in internal medicine and to promote personal relationship between internists in all countries." It is obvious that such an organization may do much to re-establish the international contacts between practitioners and teachers of internal medicine which were disrupted by World War II, and for this reason, may appeal to many American physicians.

Membership is restricted to qualified internists, who have been accepted as members of the national associations of internal medicine in their several countries. Dues are purely nominal (10 Swiss francs per annum). A substantial group of Swiss, Italian and Swedish physicians have already applied for membership, and plans for the Paris congress are proceeding under the direction of Professor A. Gigon of Basle (President of the Society), Dr. Nanna Svartz of Stockholm and Dr. L. Justin-Besancon of Paris.

American, Canadian and Latin-American physicians who may be interested in membership may direct their inquiries to Dr. A. M. Snell, 102–110 Second Avenue Southwest, Rochester, Minnesota.

7th International Congress on Rheumatic Diseases

The 7th International Congress on Rheumatic Diseases was held at the Waldorf-Astoria Hotel, New York City, May 30 to June 3, 1949, with Philip S. Hench, M.D., F.A.C.P., Rochester, Minn., as Chairman of the General Committee on Arrangements. The program included lectures, clinics and panel discussions. The participating organizations included the Ligue Internationale contra le Rheumatisma and the Pan American League for the Study and Control of Rheumatic Disease, of which organizations the late Ralph Pemberton, M.D., F.A.C.P., Philadelphia, was then President, and the American Rheumatism Association, of which Dr. Richard H. Freyberg, F.A.C.P., New York, and Dr. Edward F. Rosenberg, F.A.C.P., Chicago, are President and Vice President, respectively.

A group of about 100 physicians from foreign countries, especially European and South American, who attended the Congress, remained in the United States for a conducted tour of medical institutions here. On Saturday, June 11, they visited the headquarters of the American College of Physicians, where a scientific program was held and a buffet luncheon served. The group was in the charge of Dr. George E. Farrar, Jr., F.A.C.P., of the Philadelphia Rheumatism Association.

New Deans of Medical Schools

The successor as Dean of Harvard Medical School to Dr. C. Sidney Burwell, F.A.C.P., will be Dr. George P. Berry, Professor of Bacteriology and Associate Dean of the University of Rochester School of Medicine and Dentistry. Dr. Berry assumed his new post on July 1. He is a graduate of Johns Hopkins University School of Medicine, a diplomate of the American Board of Internal Medicine, and has served on the staffs of the Rockefeller Institute and Hospital and the University of Rochester. He is on the editorial boards of the Journal of Immunology, Bacteriological Reviews, and the Journal of Bacteriology. He is widely known for his investigations of virus diseases.

Dr. Burwell will continue in full-time teaching and research.

Richard H. Young, M.D., F.A.C.P., now Dean of the University of Utah College of Medicine, Salt Lake City, has been appointed to the Deanship of Northwestern University Medical School, succeeding Dr. J. Roscoe Miller, M.D., F.A.C.P., who became President of Northwestern University this month.

Mr. Basil O'Connor, President of the International Poliomyelitis Congress, has presented to the College Library a copy of the book, "Poliomyelitis, Papers and Discussions Presented at the First International Poliomyelitis Conference," published by J. B. Lippincott Company, Philadelphia, 1949. This book contains the papers pre-

sented at the First International Poliomyelitis Conference which was held in New York, N. Y., July 12–17, 1948. The American College of Physicians was one of the scientific organizations which officially participated in the conference.

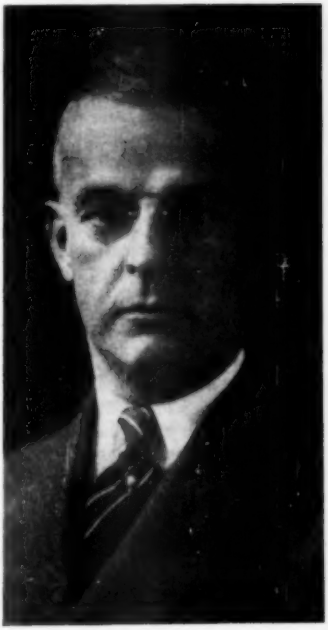
Grateful acknowledgment is made to former President O. H. Perry Pepper, M.A.C.P., Philadelphia, of his kindness in presenting to the College Library of Publications by Members a copy of "Medical Etymology," written by Dr. Pepper and published by W. B. Saunders Company, Philadelphia, 1949.

Dr. Arthur M. Master, F.A.C.P., New York City, has been elected Vice President of the Medical Society of the County of New York.

Anthony Bassler, M.D., F.A.C.P., New York City, was recently honored with a testimonial dinner on the occasion of his 50 years in the practice of medicine and in celebration of his 75th birthday. William B. Rawls, M.D., F.A.C.P., was Honorary Chairman of the dinner. Dr. Bassler was presented with a medallion by the National Gastroenterological Association, of which he was President and is Honorary President.

OBITUARIES

DR. SYDNEY R. MILLER



Early in the morning of May 25, 1949, Dr. Sydney R. Miller, of Baltimore, Md., passed away quietly in his sleep. The news of his death was not such a great shock to his friends and associates in Baltimore because he had been in failing health for the last six years.

Dr. Miller was born in Newark, N. J., August 9, 1884, received his B.S. degree from New York University, and graduated from the Johns Hopkins University School of Medicine in 1910. From 1912 to 1914 he was Director of the Laboratories of the Phipps Psychiatric Clinic. For the next ten years he was closely associated with the teaching in the Johns Hopkins University School of Medicine and on the wards of the Johns Hopkins Hospital. He later became Attending Physician of the Johns Hopkins Hospital, and Associate Professor of Medicine at the University of Maryland School of Medicine, as well as Attending Physician at the Union Memorial Hospital. Dr. Miller was also a Diplomate of the American Board of Internal Medicine, and was the author of numerous scientific papers. Dr. Miller was a member of the Zeta Phi, Phi Beta Kappa, and Alpha Omega Alpha Fraternities, The Baltimore City Medical Society, The American Medical Association, The Southern Medical Association, The American Clinical and Climatological Association, the Medical and Chirurgical Faculty of the State of Maryland, and a Master of the American College of Physicians.

In 1920 Dr. Miller became a Fellow of the American College of Physicians, and a Life Member in 1931. From 1920 to 1947 it is doubtful if any one man contributed more to the reorganization and foundation of sound policies developed in the American College of Physicians than Dr. Miller. For his great contributions to the College and to Internal Medicine he was made a Master of the College in 1947. Throughout his years in serving the College, Dr. Miller was on the Board of Regents, and his most wonderful contribution undoubtedly was to the Committee on Credentials, on which he served for many years. He was made President-Elect in 1929 and installed in the Presidency in 1930, serving through 1931. Dr. Miller was the President of the American Congress on Internal Medicine in 1922 and 1923, and with the respective Chairmen, Drs. George B. Eusterman and S. Marx White, and the late Dr. David Riesman, conducted the Sixth and Seventh Annual Sessions of the College at Rochester-Minneapolis and Philadelphia, respectively, and it was through his efforts that a meeting of the College was held in Baltimore in the year of his Presidency, 1931, which, to date, is the only time it has been held in Baltimore. It is interesting to note that this meeting was, by far, the largest Annual Session of the College up to that time in the history of the College.

Dr. Miller was a life-long friend and associate of Dr. Walter A. Baetjer. The office of Baetjer and Miller was a byword in medical circles, not only in Baltimore, but along the entire eastern seaboard. For Baltimoreans, Dr. Miller can be remembered for a great many things but, to me, there were two outstanding attributes which made him a big man. First, his interest and desire ever to help the younger man and, second, his foresight in the need of such an organization as the College. His untiring energy and interest in all the College activities have unquestionably helped greatly to place the College on such a marvelous educational basis as it is today. Even during his years of sickness, which were many, he never lost interest, and he followed the progress and the activities as though he had just been made a member. I am sure that the organization will be forever grateful for his wise counsel and coöperation.

WETHERBEE FORT, M.D., F.A.C.P.,
Governor for Maryland

DR. RANDOLPH WEST

Dr. Randolph West, a distinguished member of the American College of Physicians, died suddenly at his home of a heart ailment on May 20, 1949.

Dr. West was born in Princeton in 1890, the son of Dean Andrew Fleming West, the first dean of the Princeton Graduate School. He attended Lawrenceville Academy and then Princeton University, where he received his A.B. degree in 1912 and his A.M. the following year. He graduated from the College of Physicians and Surgeons, Columbia University, in 1917, and interned at the Presbyterian Hospital, 1917–1918. After serving in the armed forces he returned as assistant resident, then resident at that institution, and since 1922 has been associated with the Department of Medicine of Columbia University as a teacher and investigator. After a succession of advancements in academic rank he became Professor of Medicine in 1947. He was also Attending Physician at the Presbyterian Hospital and Vanderbilt Clinic.

Dr. West's most notable contributions to the science of medicine were his studies on the mechanism of anemia and on the nature of the anti-anemic substance in liver. In association with Dr. H. D. Dakin he succeeded in preparing some highly potent fractions, but was unable to crystallize the material with the methods then available. Within recent months he collaborated with the Merck chemical group in establishing Vitamin B_{12} as the active ingredient. For his constructive work on problems of anemia he was to have received the first annual Joseph Goldberger Award of the Nutrition Foundation this year.

He was a former editor-in-chief of the Journal of Clinical Investigation, and at the time of his death was chairman of the Anti-anemia Preparations Advisory Board of the U. S. Pharmacopoeia. He was a Fellow of the American College of Physicians (1937), and a member of many medical and scientific societies, including the Association of American Physicians, the American Society for Clinical Investigation, the New York Academy of Medicine, and the Society for Experimental Biology and Medicine.

Dr. West was a brilliant and inspiring teacher, an able clinician and a sound, imaginative investigator. He was beloved and admired for his kindly wit, his graciousness and for his idealism. He was truly a distinguished member of the medical profession, and a memorable individual. His associates feel deeply the loss of his stimulating wisdom and his genial philosophy.

FRANKLIN M. HANGER, M.D., F.A.C.P.

DR. SOLOMON BEN-ASHER

The death of Dr. Solomon Ben-Asher on April 27, 1949, from coronary thrombosis, closed a life devoted to medicine as a creative and affirmative form of living.

It was his creed that the total personality must be treated, not merely the diseased organ, and that the measure of healing should be gauged, not only by the degree of physical health, but also by the emotional balance to which a patient was returned. He strove to help each patient to achieve a maximum degree of usefulness within the framework of his physical handicap, since he believed this to be the best anchor to life.

Born in Kaunas, Lithuania, to a rabbinic family on December 23, 1894, he was brought to this country at the age of nine. He graduated in June 1919, from the College of the City of New York. During World War I, he served at the Washington, D. C., Experimental Station of the Chemical Warfare Service.

His student years at New York University College of Medicine were crowded since he financed his studies by an assortment of jobs which ranged from teaching to transporting jewelry across the country for the American Railway Express. His interest in medicine may be judged by the statement that for him real study of subject matter often came after the successful completion of examinations. Following his graduation in June, 1923, he served his internship at the Jersey City Medical Center and, in 1924, began practicing medicine in Jersey City. Throughout the years that followed he continued his medical studies by taking postgraduate work at Columbia University and Mount Sinai Hospital in pathology, roentgenology and other subjects. He also received training in cardiology and in gastro-enterology, and became a Diplomate of the American Board of Internal Medicine.

From 1938 to 1946, Dr. Ben-Asher served as assistant physician to the cardiac clinic of the New York University College of Medicine and as attending physician to the same from 1946 to 1947. He was an attending physician at the Jersey City Medical Center and Fairmount Hospital, and at the Greenville Hospital, where he was also attending cardiologist.

Dr. Ben-Asher combined an intense devotion to his patients often at great personal sacrifice, with a great deal of clinical investigation. He studied the value of the thiouracil compounds in angina pectoris at the cardiac clinics of the Medical Center and the Greenville Hospital, and published the results in the ANNALS OF INTERNAL MEDICINE and in the Journal of the Medical Society of New Jersey. His interest in all phases of internal medicine resulted in a number of articles, such as "The Pharmacological Action of Quinidine and Its Use in Heart Disease," "On the Toxicity of the Mercurial Diuretics," "Hypertension Caused by Renal Infarction," and "Nitrogen Mustard Therapy."

Friends and patients who were aware of his pioneering work in Zionism and of his interest in the establishment of a medical school at the Hebrew University in Jerusalem have created a memorial fund for the endowment of a laboratory or chair in his name at this institution.

ABRAHAM E. JAFFIN, M.D., F.A.C.P.

DR. SHAUL GEORGE

Shaul George, M.D., aged 75, died April 14, 1949, at Pittsburgh, Pa.

He was born in 1873 in the land formerly known as Persia, now Iran.

He received his premedical training at Valparaiso University, Ind., and then entered the Northwestern Medical School in Chicago from which he graduated in 1904.

Dr. George interned in the Pittsburgh Hospital and subsequently served as a member of its Medical Staff for many years. He took postgraduate work in Berlin and Vienna, and devoted his entire professional career to internal medicine. During World War I, he served in the Medical Reserve Corps of the United States Army.

Dr. George became a Fellow of the American College of Physicians in 1917.

CHARLES W. MORTON, M.D., F.A.C.P.,
Governor for Western Pennsylvania

DR. ANNE HEATH THOMAS

Anne Heath Thomas, M.D., who was born and spent her active life in Philadelphia, died May 21, 1949, at the age of 76 years.

After receiving her A.B. and A.M. degrees from Bryn Mawr College in 1897 and 1898, and her M.D. degree from Woman's Medical College of Pennsylvania in 1905, she did postgraduate work at the Johns Hopkins Hospital and in Vienna and in Berlin. In 1909, Dr. Thomas joined the faculty of her Alma Mater and rose to the position of Clinical Professor of Medicine and Professor of Clinical Diagnosis.

Following her retirement from active practice in 1941, Dr. Thomas removed first to Blowing Rock, N. C., and later to Colorado Springs, where her end came.

Dr. Thomas maintained medical connections in Philadelphia, being a member of the Philadelphia County Medical Society, the Philadelphia Heart Association, the Medical Society of the State of Pennsylvania, and the American Medical Association. She was elected to Fellowship in The American College of Physicians in 1949.

THOMAS M. MCMILLAN, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania

DR. ABRAHAM M. LITVAK

Dr. Abraham Myer Litvak died on January 28, 1949. Dr. Litvak was born in Russia in 1882 and came to the United States in 1907.

Dr. Litvak had studied engineering at Cooper Union and pharmacy at the Brooklyn School of Pharmacy, from which he received the Ph.G. degree in 1914. While studying pharmacy, he found that his real interest was in medicine and he entered George Washington University School of Medicine, from which he graduated in 1920. He served internships at the Volunteer and Lincoln Hospitals, and the Kingston Avenue Hospital for Communicable Diseases, in which hospital he was Resident Pediatrician until 1924 when he took up private practice. At the time of his death, Dr. Litvak was Director of Pediatrics at the Beth-El Hospital, Attending Physician and President of the Medical Board of the Kingston Avenue Hospital, and Associate in Pediatrics at the Jewish Hospital, Brooklyn.

A Fellow of the American College of Physicians since 1942, Dr. Litvak was a Fellow also of the American Medical Association and the American Academy of Pediatrics, and a member of the Medical Society of the State of New York, the Academy of Medicine of Brooklyn, and the East New York Medical Society. He was one of the most ardent workers in the Pediatric Section of the Kings County Medical Society and was honored by election to the Presidency for the years 1944–1946.

Dr. Litvak was an inspiring teacher, and young doctors constantly sought him out for counsel which he freely and unhesitatingly gave. In the conduct of his profession, he sought the honor and maintenance of high ideals and he placed scholarship and hospital work above private practice. In the conduct of his life, he lived modestly and with dignity, with goodwill toward his fellow men. His death marks a real loss to the profession.

ASA L. LINCOLN, M.D., F.A.C.P.,
Governor for Eastern New York

ABRIDGED MINUTES OF THE COMBINED EXECUTIVE SESSION OF THE BOARD OF REGENTS AND BOARD OF GOVERNORS

NEW YORK, N. Y.

MARCH 27, 1949

The Annual Joint Session of the Board of Regents and Board of Governors of the American College of Physicians convened in the Jansen Suite of the Waldorf-Astoria Hotel, New York, N. Y., Sunday, March 27, 1949, at 2:00 p.m., with Dr. Walter W. Palmer, President of the College, presiding, and Mr. E. R. Loveland acting as Secretary.

The roll was called by the Secretary, and the following were in attendance:

Officers and Regents: Walter W. Palmer, *President;* Reginald Fitz, *President-elect;* William S. Middleton, *First Vice President;* Maurice C. Pincoffs, *Second Vice President;* Charles E. Watts, *Third Vice President;* William D. Stroud, *Treasurer;* George Morris Piersol, *Secretary-General;* Ernest E. Irons, William S. McCann, T. Grier Miller, Charles F. Moffatt, David P. Barr, A. B. Brower, Alex. M. Burgess, Ernest H. Falconer (also Alternate for Governor, Northern CALIFORNIA), Cyrus C. Sturgis, Marion A. Blankenhorn, Walter B. Martin, Hugh J. Morgan, LeRoy H. Sloan, George F. Strong, and Walter L. Palmer, *Chairman, Board of Governors.*

Governors: Leland P. Hawkins, Los Angeles, CALIFORNIA (Southern); * Louis S. Faust, Denver, COLORADO; Thomas P. Murdock, Meriden, CONNECTICUT; Wallace M. Yater, Washington, DISTRICT OF COLUMBIA; Cecil M. Jack, Decatur, ILLINOIS (Southern); Robert M. Moore, Indianapolis, INDIANA; Harold H. Jones, Winfield, KANSAS; Chester S. Keefer, Boston, MASSACHUSETTS; Joseph D. McCarthy, Omaha, NEBRASKA; Edward C. Reifenstein, Sr., Syracuse, NEW YORK (Western); * Bert F. Keltz, Oklahoma City, OKLAHOMA; Edward L. Bortz, (Vice Chairman), Philadelphia, PENNSYLVANIA (Eastern); R. R. Snowden, Pittsburgh, PENNSYLVANIA (Western); John L. Calene, Aberdeen, SOUTH DAKOTA; William C. Chaney, Memphis, TENNESSEE; Louis E. Viko, Salt Lake City, UTAH; Herbert K. Detweiler, Toronto, ONTARIO; * Elmer R. Smith, Ancon, REPUBLIC OF PANAMA and the CANAL ZONE; Arless A. Blair, Fort Smith, ARKANSAS; Benjamin F. Wolverton, Cedar Rapids, IOWA; Edgar Hull, New Orleans, LOUISIANA; Douglas Donald, Detroit, MICHIGAN; * Harry L. Smith, Rochester, MINNESOTA; Ralph A. Kinsella, St. Louis, MISSOURI; Harry T. French, Hanover, NEW HAMPSHIRE; George H. Lathrope, Newark, NEW JERSEY; Paul F. Whitaker, Kinston, NORTH CAROLINA; Robert B. Radl, Bismarck, NORTH DAKOTA; Ellsworth L. Amidon, Burlington, VERMONT; J. Edwin Wood, Jr., Charlottesville, VIRGINIA; George Anderson, Spokane, WASHINGTON; Delivan A. MacGregor, Wheeling, WEST VIRGINIA; * Hugh A. Farris, St. John, MARITIME PROVINCES; Arthur T. Henderson, Montreal, QUEBEC; Jose J. Centurion, Havanna, CUBA; E. Dice Lineberry, Birmingham, ALABAMA; Leslie R. Kober, Phoenix, ARIZONA; Lemuel C. McGee, Wilmington, DELAWARE; Carter Smith, Atlanta, GEORGIA; Samuel M. Poindexter, Boise, IDAHO; J. Murray Kinsman, Louisville, KENTUCKY; Richard S. Hawkes, Portland, MAINE; Wetherbee Fort, Baltimore, MARYLAND; Harold W. Gregg, Butte, MONTANA and WYOMING; Asa L. Lincoln, New York, NEW YORK (Eastern); Charles A. Doan, Columbus, OHIO; Howard P. Lewis, Portland, OREGON; David W. Carter, Jr., Dallas, TEXAS; Karver L. Puestow, Madison, WISCONSIN; Charles H. A. Walton, Winnipeg, MANITOBA and SASKATCHEWAN; * James O. Gillespie, UNITED STATES ARMY; Clifford A. Swanson, UNITED STATES NAVY; Paul B. Magnuson, UNITED STATES VETERANS ADMINISTRATION.

* Alternate.

The Secretary read abstracted Minutes of the meeting of the Board of Regents held at Philadelphia on November 7, 1948, and of the last meeting of the Board of Governors held at San Francisco, Calif., on April 21, 1948.

The President declared the Minutes approved as read, since there were no questions, suggestions or corrections.

The Secretary then presented the following communications:

(1) A letter of regret from Dr. George Dock, F.A.C.P., Altadena, Calif., stating he could not be present at the Convocation to receive a Mastership which had been awarded to him by vote of the Board of Regents on November 7, 1948.

(2) Communications from Dr. Francis G. Blake, F.A.C.P., and Dr. Robin C. Buerki, F.A.C.P., of the Advisory Council on Medical Education, stating the Council was being reactivated and requesting the College to re-establish representation thereon.

After general discussion, it was moved, seconded and carried that the American College of Physicians, through the President, shall appoint a representative to attend meetings of the reactivated Advisory Council on Medical Education for the first year to determine its purposes and policies, and to determine further what may be contributed to its work by the College. (President Palmer thereafter appointed Dr. Marion A. Blankenhorn.)

(3) A communication from the National Society for Medical Research, signed by Dr. A. J. Carlson, President, and Dr. A. C. Ivy, Secretary-Treasurer, requesting that the College become a member organization of said Society. While no dues are exacted, the Society's program is supported by contributions of $25.00 to $1,000.00 from its member groups and from commercial concerns. The communication had first been reviewed by the Committee on Fellowships and Awards of the College, and unanimously recommended that the College become a member organization, but made no recommendation with regard to financial contributions.

By motion regularly made and seconded, the College accepted the invitation to become a member organization. Dr. Reginald Fitz, Chairman of the Committee on Fellowships and Awards, was asked to comment further:

DR. FITZ: "The National Society for Medical Research is concerned with the propaganda on vivisection that is going around the country, and as one way of meeting that, this organization was formed and is being supported in a variety of ways. In Massachusetts, and possibly in other states, the anti-vivisectionists are spending a lot of money in trying to get legislation which we feel would practically prevent modern experimental medicine from going forward. I believe what Dr. Ivy asks for is perfectly reasonable, and that the College should subscribe to it and go on record as believing that the whole future of medicine has to go forward with the further experimentation in medicine. Dr. Ivy would like us to lend our name and possibly offer any financial support we would like to add."

There was general assent to the support for this organization, but no specific action was taken with regard to a financial contribution.

(4) The Secretary had been asked to report on the status of the deductibility of costs of Postgraduate Courses in connection with Federal Income Taxes. He had continued the investigation through Senator Eugene D. Millikin, Chairman of the Senate Finance Committee, who in turn consulted the Chief of Staff of the Joint Committee on Internal Revenue Taxation, who reported briefly as follows:

"The pertinent facts in the case of the Postgraduate Courses under question seem to be:

"(a) They are educational in character.

(b) They are available only to persons who have received their medical degree and, insofar as they are limited to members of the American Colege of Physicians, are limited to individuals who have shown competence in their field.

(c) They are designed to keep members of the American College of Physicians and other doctors up to date with medical progress in this field.

"Based on these facts it is my opinion that the expenses for these Postgraduate Courses are properly deductible under present law. It would be necessary, however, to go to the courts to establish this fact. The Bureau of Internal Revenue, as the letter from the Commissioner indicated, would not allow their deduction. The Bureau's position is based on the fact that Section 29.23 (a)-15 of the regulations states:

> 'Among expenditures not allowable are the following: . . .
> expenses of taking special courses or training. . . .'

"I believe, however that the regulations in this respect go too far. Section 23 (a) (2) of the Code provides for the deduction of '. . . all the ordinary and necessary expenses paid or incurred during the taxable year for the production or collection of income. . . .' Moreover, with respect to property, Section 23 (a) (2) provides for the deduction of expenses attributable to 'conservation or maintenance.'

"It is not suggested that this provision of the law permits the deduction of any educational expenses incurred in order to place an individual in a position to earn income. These are capital outlays and if they were deductible at all, they would necessarily be taken over a period of years in the form of depreciation. Depreciation, however, is limited to property. Thus, educational expenditures incurred in order to place an individual in a position to earn income are not deductible.

"However, the educational expenditures with which the American College of Physicians is concerned are not of that type, according to their letter. They rather are designed to keep doctors abreast of the current developments in their special fields. They are ordinary and necessary expenses incurred in the production or collection of income. Moreover, since they merely keep the doctors abreast of the developments in their fields, they are currently expendable, and, therefore, are expenses rather than capital outlays.

"There is precedence in present Bureau practice for allowing deductions for educational expenses to keep abreast of current developments. At the present time the Bureau allows the deduction of expenses incurred for trade periodicals or magazines, which in reality are just another form of current-development educational expenses. Moreover, the conference or convention expenses, which are allowed as deductions, are in large part current-development educational expenditures. It is sometimes contended that the deduction of these latter expenditures are allowed because they are necessary in developing or maintaining business contacts. However, in many cases the value of the conventions from this point of view is almost non-existent, and in many other cases it is of little importance. Yet no attempt is made on the part of the Bureau to deny the deduction of convention expenses which are of value largely from the educational standpoint."

The Secretary thereafter had consulted the College counsel for advice. It was the counsel's opinion that to prosecute a test case through the tax courts of the United States, or through the district court of the United States, and probably through the Circuit Court of Appeals, would require at least two years, and, furthermore, he was not sanguine about the results even then, and he inclined to the opinion that the time and expense involved in the test case would not be warranted, and would cost no less than $1,000.00. He suggested, however, that we await decision of the tax court in the case of Nora Payne Hill (a test case now in progress), and if the final decision in that case is unfavorable to the taxpayer, he believes that legislative action would be necessary to establish the right of this deduction.

(5) A report from the Secretary concerning the publication of a Directory of the College. The Board of Regents at its previous meeting had authorized the publication

of a new and revised Directory of the College, provided a minimum of two thousand pre-publication orders were obtained. The Secretary reported that more than the minimum number of orders had been received, and the Executive Office would proceed with the publication of the Directory in the early summer and autumn months.

(6) Request for the appointment of a Committee to draw up a Certificate for Honorary Fellowships. In view of the fact that the By-Laws were about to be amended, already approved by the Board of Regents, it was pointed out that there should be a Committee appointed to draw up the formal Certificate of Honorary Fellowship.

On motion by Dr. A. B. Brower, seconded by Dr. Alex. M. Burgess, and regularly carried, the President was authorized to appoint such a Committee. The appointment of the Committee was left to the incoming President.

(7) A communication from the United States Pharmacopoeial Convention, asking the College to appoint not exceeding three delegates, and three alternates, to the meeting of the Convention in Washington in 1950.

It was pointed out that the College has had representation on each occasion on which the revision of the Pharmacopoeia took place.

On motion by Dr. Walter B. Martin, seconded by Dr. A. B. Brower, and unanimously carried, it was

RESOLVED, that the incoming President shall make such appointments on behalf of the College.

President Walter W. Palmer called for the report of the Secretary-General, Dr. George Morris Piersol.

Dr. Piersol thereupon reported the deaths and read the names of thirty Fellows and three Associates since the last meeting of the Board of Regents. The Boards thereafter arose and observed a moment of silence.

Dr. Piersol, continuing his report, stated that sixty-five Fellows have been added to the Life Membership Roll, making a total of 785, of whom 62 are deceased, leaving a balance of Life Members of 723. Names of the new Life Members were spread upon the Minutes.

Dr. Piersol then continued, as Chairman of the Committee on Credentials, and presented a report of meetings of the Committee at Philadelphia on February 26, 1949, and at New York on March 26, 1949.

In accordance with recommendations of the Committee, numerous routine problems were disposed of, 175 candidates (names previously published in these columns) were elected to Fellowship and 217 candidates (names also previously published in these columns) were elected to Associateship.

It should here be recorded that while elections were officially made by the Board of Regents, discussions were open to members of the Board of Governors, and they readily entered into the discussions of candidates and problems of the Credentials Committee.

At this point Dr. Piersol reported an analysis of the candidates considered on February 26, 1949, and on March 26, 1949, as follows:

(1) February 26, 1949:

A. Candidates for ASSOCIATESHIP:

Recommended for Election	126	
* Fellowship Candidates Recommended for Election first to Associateship	11*	137
Recommended for Election to Direct Fellowship		1
Deferred		36
Rejected		32
		195, plus *11

B. Candidates for FELLOWSHIP:

Recommended for Advancement to Fellowship	98	
Recommended for Election Directly to Fellowship	23	121
* Recommended for Election first to Associateship		11
Deferred		56
Rejected		5
		193

(2) March 26, 1949:

A. Candidates for ASSOCIATESHIP:

Recommended for Election	74	80
* Fellowship Candidates Recommended for Election first to Associateship	6 *	
Deferred		9
Rejected		1
		84, plus *6

B. Candidates for FELLOWSHIP:

Recommended for Advancement to Fellowship	48	
Recommended for Election Directly to Fellowship	6	54
* Recommended for Election first to Associateship		6
Deferred		16
Rejected		2
		78

Dr. Piersol then presented the following report on candidates elected to Associateship on April 1, 1944, whose five-year maximal period now expires, unless they served on military duty during the War after their election:

Advanced to Fellowship	54
Resigned	1
Rejected	10
Term Extended because of Military Service	19
TOTAL, Candidates Elected April 1, 1944	84

Dr. Piersol at this point presented the following report on a combined meeting of the Committee on Credentials and the Executive Committee of the Board of Regents, held at New York on March 26, 1949:

"In accordance with the resolution of the Board of Regents passed on April 20, 1948, and reaffirmed at their meeting on November 7, 1948, the Committee on Credentials and the Executive Committee met at 2:00 p.m., in New York City on March 26, 1949, to consider certain suggestions that had been made in reference to change in membership of the College.

"The first proposal considered was whether the membership of the College should be restricted to Internists. After a thorough discussion of this subject, it was moved, seconded and carried, that the Committee recommend to the Board of Regents that it is neither necessary nor desirable at this time to eliminate for membership in the College the specialties allied to Internal Medicine that may now be admitted to membership.

"Inasmuch as the above suggestion was made in order to reduce the size of the College, it was suggested that this could be accomplished by restricting attendants at the Annual Session of the College to members of the College and especially invited guests. It was felt, however, that this would be undesirable. The motion to recommend such a restriction was lost.

"In the course of discussion, it was brought out that at present guests may attend meetings of the College upon the payment of a fee of $15.00, which entitles them to essentially all the rights and privileges of the Associate or Fellow, including a year's subscription to the ANNALS OF INTERNAL MEDICINE. Inasmuch as such an arrangement seems unfair to the membership of the College, it was moved, seconded and carried that the Committee recommend to the Board of Regents that in the future the fee for a guest at an Annual Session be increased, the amount of such increase to be left to the discretion of the Board of Regents.

"At the meeting of the Board of Governors, held in San Francisco on April 21, 1948, it was suggested that it might be desirable to eliminate Associate membership in the College. It was moved, seconded and carried that the Committee recommend to the Board of Regents that Associate membership should be retained. A year ago it was recommended to the Board of Regents that certification by a recognized board of certification be made a prerequisite for election to Associateship in the College. It was moved, seconded and carried by the Committee that they recommend to the Board of Regents that certification as a prerequisite for Associateship should not be required.

"The question of the length of time of Associateship was brought before the Committee for discussion. It was moved, seconded and carried that the Committee recommend to the Board of Regents that the present five-year term of Associateship be retained.

"The present form of the proposal blank for membership in the College was discussed. It was moved, seconded and carried that the Committee recommend to the Board of Regents that the present form of the proposal blank be retained.

"The Committee entered into a detailed discussion of specific requirements over and above certification by a recognized board that should be considered as qualifications for election to Fellowship. The present practices of the Credentials Committee and numerous suggestions were carefully reviewed. In order to make the problem of the qualifications for Fellowship clearer, it was moved, seconded and carried that the Committee recommend to the Board of Regents that the Executive Secretary be directed to draw up a letter setting forth in some detail requirements for election to Fellowship, that this letter be reviewed by the Credentials Committee and sent to Governors and candidates for Fellowship."

Dr. Reginald Fitz moved the acceptance of the report. It was seconded by Dr. Paul F. Whitaker, and opened for discussion.

DR. ALEX. M. BURGESS: "Having been on the Board of Governors for a good many years and now being on the American Board of Internal Medicine, I am particularly cognizant, as I think some of you are, too, of the implication which the maintenance of the status quo brings about. If we adopt the recommendations of the Executive Committee and the Committee on Credentials, we should do it knowing what we are doing.

"We are assailed by letters quite frequently from individuals who are in a quandary. On the advice of their Governor they have applied for Associateship early. When they get within about two years of their five-year maximum, they have been notified by the Credentials Committee that they must qualify for Fellowship. Not until then do some of them attempt to pass the examinations of the American Board of Internal Medicine.

"Now I call to your attention the fact that the American Board of Internal Medicine has a written examination only once a year. If the candidate misses one, it is a full year until the next one comes. A person at the present time can apply three

times to take the examination in order to pass, and then he must pass an oral examination too. Now take an Associate who waits for his first three years and then takes his board. He may take it with a year to spare, but suppose he fails the first written examination. He takes it a second time a year later, and if he fails this time, he is all through, so far as qualifying for Fellowship within his maximum term is concerned. He hasn't even got a chance yet to take the oral.

"If you had anything to do with constructing these examinations and realize that we see Associate Professors of Medicine failing right along with everyone else, men who are excellent physicians, but perhaps a little bit too specialized, it is no real discredit if they fail once or twice. It may easily take three or four years for good men to attain certification. Under the current rules of the College their Associate terms in the meantime would have expired and they are out. I think we do an injustice to a good many men who are coming up for Fellowship right along. We ought to extend the term of Associateship or freeze a man's status until he has exhausted his ability to attain certification, or do something to prevent dropping these men as Associates and from the College for all time. It is an injustice to good men."

Dr. George Morris Piersol: "The Committee considered this very point at considerable length, and were led to make the recommendation they did for two reasons —first, in the last three years the number of candidates for Associateship who have already been certified by their respective boards has been steadily increasing. Three years ago about 40 per cent of the candidates had been certified. This past year 56 per cent had been certified, and in the last group there were 75 per cent who were certified; second, recognizing the fact that it would be unfair to take a man as an Associate who hadn't even at that point reached the stage where he was qualified for admission to the Board examinations, the Credentials Committee is careful in determining two things about candidates for Associateship: (a) whether they are already certified; (b) if not certified, they should not be elected unless at the time of their proposal they already have fulfilled the requirements necessary for admission to the examination."

Dr. Asa L. Lincoln: "Might it not be possible to reconsider men who fulfill all the qualifications for advancement to Fellowship save only certification, and if, as and when they fulfill the certification requirement, they may be elected to Fellowship; or, do they ever have an opportunity of being considered again? If so, do they have to return to the College as Associates and serve another minimal three-year term?"

Dr. Piersol: "If a man fails to qualify for advancement to Fellowship and is dropped, there is no provision for extending his Associate term, except for exceptional, extenuating circumstances, such as illness. If it were established that any man who fails to attain certification could apply for an extension of time, a large percentage of the Associates might readily take an indeterminate period of time, asking successively for extension. The rules and regulations adopted two or three years ago by the Board of Regents on the recommendation of the Survey Committee, headed by Dr. William S. Middleton, expressly state that a man who has failed to become a Fellow within the prescribed length of time must be dropped, and he cannot be proposed for direct Fellowship thereafter. Formerly that was a loophole used entirely too frequently, but is now eliminated by the new regulations. At the present time if a candidate does not qualify in five years, except for a good and legitimate reason and not procrastination, indolence or indifference, he must be dropped."

Dr. George H. Lathrope: "Much of this trouble can be avoided for the Credentials Committee and for the Governors if the Governors would get this point firmly in mind, that a man when he is proposed for Associateship is clearly eligible for admission to his Board examinations. Another thing, a candidate ought to be established in one location for more than just a few months. The Committee would prefer not to have them proposed until they have been in practice for two years in one place."

Dr. Burgess: "Mr. President, Dr. Piersol's explanation of the guarding action of the Credentials Committee certainly is well and good for the future. Those that I am interested in are the candidates who have been ill-advised in the past and became Associates before the current rule was put into effect. I think this College ought not knowingly do any injustice to even one candidate."

Dr. Piersol: "There may be some individuals who feel that they are part of that group, but I am unable to say. The present rule is not really too recent a decision. The Committee has been operating with this thought in view for a long time. There will always be candidates who, in spite of the fact that they have to do a certain given thing in a certain length of time, will procrastinate. They have no particularly good reason. I do not entertain too much compassion for them. They knew when they started what they had to do. The Governors knew, and everybody knew. Most young men today have certification as their dominant interest. They are very much aware of the necessity of certification. I doubt if we shall find very many who will be dropped because they didn't know they had to be certified in five years."

Secretary E. R. Loveland: "In defense of the Credentials Committee, I know perhaps of four or five cases where candidates were dropped for failure to complete certification in the five-year period, but in which the Credentials Committee thought the circumstances made the cases somewhat excusable, and, thereafter, when these candidates attained certification, recommended them for reinstatement as an Associate for a period of one year, in order that they could present their credentials for Fellowship. I feel reasonably sure that the number of Associates who are dropped for failure to qualify for certification is less than 5 per cent."

President Walter W. Palmer: "I would remind you also that the recommendations of the Committee provide for a special letter to each new Associate, clearly stating what he must accomplish in the next five years."

Dr. Chester S. Keefer: "Mr. President, it has always seemed to me that a great many problems would be abolished if we did away with Associateship altogether. We have heard today that an increasing number of men have already attained certification before proposal for Associateship. Many misunderstandings and confusion arise among Fellows who propose candidates when the Governor is unable to endorse the candidate, or when the Credentials Committee fails to recommend his election. It seems to me that it would be well for the Regents and Governors to consider once again the question of qualifications for Associateship, and I recommend that the letter that is to be drafted by the Executive Secretary and the Credentials Committee shall include not only the exact requirements for Fellowship, but the requirements for Associateship as well."

Dr. E. Dice Lineberry: "I think that we Governors have been at fault in not eliminating candidates for Associateship until they are clearly eligible."

At this point President Palmer asked for a combined vote of the Governors and Regents on the resolution, and it was approved unanimously.

Dr. LeRoy H. Sloan reported for the Conference Committee on Graduate Training in Medicine, saying that he had attended meetings at headquarters of the Council on Medical Education and Hospitals of the American Medical Association. The Committee has been reactivated and is now under the direction of Dr. William S. Middleton as Chairman, and there is a very active program for the inspection of hospitals all over the country. The proposal had been made through Dr. Sloan that the College appropriate some money to the Council for its contribution to the project. He pointed out again that this is a combined Committee made up of representatives of the American Board of Internal Medicine, the Council on Medical Education and Hospitals of the American Medical Association and the American College of Physicians.

Dr. Walter B. Martin reminded the Board that there had been two difficulties—one, insufficient funds to pay the inspectors, and the other the difficulty of getting

experienced and trained personnel to make adequate inspections. He inquired whether the problem of finances has been solved, assuming that the College were to make a reasonable contribution, and, second, whether an adequate number of qualified inspectors are available.

Dr. Sloan said he understood that both full-time and part-time inspectors had been procured and are actively at work.

Mr. Loveland reported that the College had been asked to furnish a list of part-time inspectors from the College, but had never heard whom they selected.

Dr. Sloan reported that at the last Conference Committee's meeting they had gone over the list to make selections. Anticipated cost of inspections was established to be between $25,000.00 and $37,500.00. The proposal, he said, was not a year-by-year contribution, but a lump sum that the College might contribute toward bringing up the backlog of inspections to date.

On motion by Dr. LeRoy H. Sloan, seconded by Dr. William D. Stroud, and unanimously carried, it was

RESOLVED, to accept Dr. Sloan's report and refer the matter of a financial contribution by the College to the Finance Committee.

Dr. Reginald Fitz, Chairman, then presented the following report for the Committee on Fellowships and Awards:

"Mr. President, this report falls into two parts. The first is merely informational. At the present time the six Research Fellows that were appointed to begin work on July 1, 1948, are all at work, and are going along well. Seven new Research Fellows were appointed by the Regents during November, 1948, to start work on July 1, 1949. Fellows from different schools are being spread about in different parts of the country under our plan. Actually eight Research Fellows were appointed last November, but one had to withdraw on account of illness. The remaining seven have expressed very enthusiastically their gratitude for the opportunity afforded by the College. The Committee also wants to put into the record the fact that the assistance of Mr. Pindar in making the work of the Committee go forward successfully has proved a very important addition to the work of the College."

The Board was unanimous in adopting this part of the report.

DR. FITZ (Continuing): "The second part of the report is more complicated. It deals with the Latin-American Fellowship Program, on which we are about to embark with the Kellogg Foundation. Copies of the plan worked out with Dr. Horning, Director of the Division of Medicine of the Kellogg Foundation, have been placed in your hands. By authorization of the Regents on the seventh of November, 1948, the plan was submitted to the Executive Committee of the Regents and was subsequently approved, but it now must be presented to the Board of Regents for confirmation and recording in the Minutes.

(Dr. Fitz proceeded to summarize the duplicated proposal in the hands of the Board.)

"The Committee feels that this really represents a very interesting new development on the part of the College, and, therefore, approves it. The Executive Committee also approves it."

Approval of the proposal was moved by Dr. Reginald Fitz, seconded by Dr. Hugh J. Morgan, and opened for discussion.

DR. CYRUS C. STURGIS: "I think the proposal should be approved, and I would like to make it clear that this project does not cost the American College of Physicians anything. All expenses will be borne by the Kellogg Foundation, but the College will have a number of very definite responsibilities. In the first place, the final selection of the men for the scholarships rests with the College, even though the group has been carefully screened in advance. Secondly, the College must select the educational institutions where the men will work, and I would like to propose that the

Committee on Fellowships and Awards be authorized by the Board of Regents and the Board of Governors to make the final selection of the candidates and to select the educational institutions to which they will be sent."

DR. WILLIAM S. MIDDLETON: "I am exceedingly interested in this program, which I think is very constructive and a very promising one. There is one element that concerns me presently, and that is the failure to take into account illness. The proposal says the sponsoring agencies do not assume financial responsibility for illness or accident. Our university had to assume responsibility for illness on some students it accepted."

DR. FITZ: "That point has been pretty well established. My understanding is that if a fellow who is assigned to any institution where students were asked to pay some kind of a health insurance fee for acute temporary illness, that would probably be arranged through the Kellogg Foundation. The intent was to make the plan very plain that if he came to this country and became ill, it wouldn't be up to the institution in which he was to work to be responsible for the cost of any prolonged illness."

DR. MIDDLETON: "I should like to see that put positively as the responsibility of the Kellogg Foundation."

DR. STURGIS: "The Kellogg Foundation has never failed to provide for illness, and they assure us that they will now see that these men receive medical attention. They prefer the statement as made in the proposal, however."

DR. MILLER: "How is the College going to make its selections?"

DR. FITZ: "Fellows shall be selected by representatives of the College and the Kellogg Foundation, in coöperation with local selection committees established in each country by the U. S. Department of State. Availability of these fellowships would be publicized in Latin-American countries, and those who wish to apply would first be screened by local committees, including the representative of the Kellogg Foundation, as carefully as possible. After this screening the candidates would be submitted to the College for final decision."

The resolution was then presented for vote and unanimously carried.

Dr. Edward L. Bortz reported for the Advisory Committee on Postgraduate Courses and the Committee on Educational Policy, stating that approximately one thousand physicians had been in attendance in our courses during the past year, and that six hundred will be in attendance on the spring 1949 courses, nine in number. He stated that the Committee wished to reaffirm the policy of the College that courses should be carried on and given in the place of residence of the Director and the institution coöperating with the College.

On motion by Dr. Edward L. Bortz, seconded by Dr. George Morris Piersol, and unanimously carried, the recommendation was approved.

The Committee had carefully reviewed proposed courses for the autumn of 1949 and the spring of 1950, and proposed a program of courses for the autumn of 1949, subject to the approval of the Board of Regents and the acceptance of the various Directors and institutions. (The group of recommended courses was approved by resolution, and has already been announced in this journal.)

Dr. Bortz, by way of information, stated the Committee was working on the possibility of the following courses for 1950:

(1) INTERNAL MEDICINE. University of Pittsburgh. Dr. R. R. Snowden, F.A.C.P., Director.

(2) INTERNAL MEDICINE WITH EMPHASIS ON PATHOLOGICAL PHYSIOLOGY. University of Cincinnati. Dr. Marion A. Blankenhorn, F.A.C.P., Director.

(3) DIABETES AND GENERAL MEDICINE. New England Deaconess Hospital, Boston. Dr. Elliott P. Joslin, M.A.C.P., Director.

(4) CLINICAL ALLERGY. Roosevelt Hospital, New York. Dr. Robert A Cooke, F.A.C.P., Director.

(5) MECHANICS OF DISEASE. Peter Bent Brigham Hospital, Boston. Dr. George W. Thorn, F.A.C.P., Director.
(6) GASTRO-ENTEROLOGY. Graduate Hospital of the University of Pennsylvania, Philadelphia. Dr. Henry L. Bockus, F.A.C.P., Director.
(7) GASTRO-ENTEROLOGY. University of California and Stanford University. Dr. Dwight L. Wilbur, F.A.C.P., and Dr. Theodore L. Althausen, F.A.C.P., Directors.
(8) PHYSIOLOGICAL BASIS OF MEDICAL PRACTICE OF HEMATOLOGY. University of Utah, Salt Lake City. Dr. Max M. Wintrobe, F.A.C.P., Director.
(9) PHYSIOLOGICAL BASIS FOR INTERNAL MEDICINE COMBINED WITH MEDICAL ASPECTS OF ATOMIC ENERGY EMPHASIZING USE OF RADIOACTIVE ISOTOPES IN CLINICAL RESEARCH AND ALLIED PROBLEMS. University of Rochester.
(10) PHYSIOLOGICAL BASIS FOR INTERNAL MEDICINE. University of Toronto. Dr. Ray F. Farquharson, F.A.C.P., Director.

The report of the Committee was by resolution approved as a whole.

Dr. William D. Stroud, Chairman, presented the following report for the House Committee, which was by resolution approved:

"In accordance with directions and budget authorizations of the Board of Regents, the House Committee is gratified to report that the furnishings of the Assembly Room, including chairs, lectern, coat and hat racks and smoking stands, have been purchased and delivered. The Assembly Hall will be used in May for a group of approximately one hundred pursuing a College Postgraduate Course in Cardiology.

"The Committee also reports that the plumbing in the Men's Lounge Bathroom, and the painting and papering of rooms on the second floor, as authorized, have been completed in a very satisfactory manner; also that the electrical work and redecorating have been completed in the basement Recreation Room."

President Palmer announced that this concluded the agenda for the Regents' portion of the meeting, and called upon Dr. Walter L. Palmer, Chairman of the Board of Governors, for a report.

Dr. Walter L. Palmer stated that responsibility for the Regional Meetings rests with the Governors. In the year of 1948 there were 23 Regional Meetings with an attendance of about 2,800 men. In 1949, thus far, there had been 6 meetings held and one more scheduled. President Palmer had given very generously of his time in attending 7 of these Regional Meetings. Others of the Officers and Regents had likewise attended some of the meetings. Dr. Palmer said there is no longer concern about the Regional Meetings interfering with the Annual Sessions in any manner. The style of the Regional Meetings had been quite varied—some small with intimate groups, and others larger Regional Meetings involving several States. The type of the meeting is left entirely to the discretion of the Governor. The Executive Office of the College stands prepared to print and mail programs, furnishing postage, supplies and to contribute up to $250.00 per meeting toward other expenses.

Dr. Palmer then discussed the functions of the Governor, the most important of which is the endorsing of candidates to the Committee on Credentials. He expressed satisfaction that some of the problems had been settled at this meeting, at least temporarily. He asked the members of the Board of Governors if any had comments or reports to make.

Admiral Clifford A. Swanson arose and discussed at length the doctor situation in the Armed Forces, saying in part:

"We have the largest peace-time Army and the largest Navy in the history of our Country. In fact, the Army, considering the Air Force with it, is much larger than pre-World War II. The American Navy is six times greater than it was before the last War. With this great increase in size, there is a shortage of doctors, more so

in the Army than in the Navy. I speak for the whole military establishment. In the Navy we have all the dentists that we need. In the Army and Air Force they have 20 per cent of the dentists they need. In fact, at the present time the Army and Air Force are hiring German dentists to take care of our troops in Europe. They are also hiring German doctors to take care of our troops in Germany. I personally think it is up to us, the American doctors, to take care of our own people, especially outside of the Continental United States. We in the Navy are going to return about nine hundred young doctors to civilian life, now and up to the first of August. That will leave us approximately five hundred doctors short in the Navy. The Army will be about fifteen hundred doctors short at that time and two thousand doctors short by September.

"There are a number of doctors in the Country who should and are obligated to help, and I think that you here assembled can prevail upon these people to come into the Armed Services and spend several years there, until we get over the cold War. There are eight thousand young doctors in the United States who have received their education wholly, or in part, at Government expense. None of these eight thousand doctors have served one day in the Armed Forces. There were additionally seven thousand doctors permitted to continue their medical education during the War, not exposed to the hazards of War. From this group of fifteen thousand doctors we should prevail upon some of them to enter the Armed Services. We have organized a campaign that has been going two weeks, but it hasn't been going too well. We had sixty volunteers in the Navy. We need four hundred more. The Army needs fifteen hundred. I, for one, do not subscribe to a draft. Our military service in time of peace would rather have the medical profession rise to the occasion, which they have at all times during War, and they ought to rise to it now. Our procurement is coming along fine in normal channels. We had seven hundred applicants for two hundred openings. I think we can work out the situation in two or three years. We have to be helped now. If something doesn't happen, I am afraid Congress will take the matter into their own hands. I hope you will all prevail upon these men to do their duty for our Country now."

Dr. Maurice C. Pincoffs: "May I say a word on this subject as a member of the Medical Advisory Committee for Defense? Its responsibility is two-fold—one, to encourage the voluntary enlistments of the same group about which Admiral Swanson spoke, and also in conference with the Surgeon General to reduce as far as possible the work load of the Armed Forces, so that they will require as few medical additions as is possible. This is going forward very actively. The greatest economy in the use of medical officers is rapidly being achieved. Many of these young men are in teaching and in other voluntary hospital positions of some kind or other, and it is going to be something of a sacrifice, if they do get leave from these institutions, when they have hospital residencies coming to them. The University of Maryland is taking cognizance of that, and our faculty has assured those young men entering the first of June, leaving a promised hospital residency, that their places will be held open when they return later. That kind of backing on the part of hospitals may save the profession from having a draft of doctors, a thing that has never happened in the profession before, and which certainly would do the cause of medicine no good at this time, especially since it is so much under attack."

Dr. Paul F. Whitaker discussed the problem in North Carolina, estimating a shortage of doctors from 25 per cent to 30 per cent, and bespeaking the training of a larger number.

Adjournment.

Attest: E. R. Loveland,
Secretary

ABRIDGED MINUTES, BOARD OF REGENTS

NEW YORK, N. Y.

MARCH 29, 1949

The second meeting of the Board of Regents during the 30th Annual Session of the American College of Physicians convened at 12:30 o'clock, March 29, 1949, at the Waldorf-Astoria Hotel, New York, N. Y., with Dr. Walter W. Palmer, President, presiding, with Mr. E. R. Loveland acting as Secretary, and with the following in attendance:

Walter W. Palmer, *President;* Reginald Fitz, *President-Elect;* William S. Middleton, *First Vice President;* Charles E. Watts, *Third Vice President;* William D. Stroud, *Treasurer;* George Morris Piersol, *Secretary-General;* William S. McCann, T. Grier Miller, Charles F. Moffatt, David P. Barr, A. B. Brower, Alex. M. Burgess, Ernest H. Falconer, Cyrus C. Sturgis, Walter B. Martin, Hugh J. Morgan, LeRoy H. Sloan, George F. Strong, and Walter L. Palmer, *Chairman, Board of Governors.*

The Secretary read an abstract of the Minutes of the joint meeting of the Board of Regents and of the Board of Governors on Sunday, March 27.

The Chairman called for the report of the Committee on Finance, Dr. A. B. Brower, Chairman.

DR. A. B. BROWER: The full Committee on Finance met on Monday, March 28, 1949, at 10:00 a.m. We would first like to call your attention to the Auditor's Report for 1948.

(1) Salient Data:

(a) All accounts fully audited by Certified Public Accountant.

(b) Increase in Funds:

	Balance Jan. 1, 1948	*Increase (Net)*	*Balance Dec. 31, 1948*
General Fund	$270,570.82	$29,045.79	$299,616.61
Endowment Fund ...	246,284.89	24,055.73	270,340.62
Bruce Fund	10,000.00		10,000.00
Brower Fund	2,500.00	2,500.00	5,000.00
	$529,355.71	$55,601.52	$584,957.23

(c) Gross Assets of the College—$664,158.63.

(d) Endowment Fund Data:

Life Membership Fees, 1948, amounted to $20,385.00 (a decrease from 1947—$28,386.67).

Profit on Endowment Fund Security Transaction, $375.73.

Donation, Dr. A. Blaine Brower, second installment, $2,500.00.

(e) General Fund Data:

	1947	*1948*
Total Income	$194,667.35	$206,200.49
Total Expenses	151,139.01	164,385.41
	$ 43,528.34	$ 41,815.08

In your hands you have Detailed Financial Statements, which disclose all details and give a certified registry of all investments.

The Investment Counselor's Report and Recommendations are as follows:

(1) Analysis, as of March 10, 1949 (including Bruce and Brower Funds with Endowment):

	Endowment Fund	*General Fund*	*Total*
Market Value	$300,980.75	$190,243.22	$491,223.97
Book Value	304,291.20	187,504.22	491,795.42
Depreciation			$ 571.45

(One year ago there was an appreciation of $35,941.72 on an even smaller total investment.)

Current average yield, 4.05% (for 1947, 4.01%).

. . . Sections 2, 3 and 4, which followed detailed recommended purchases and sales of securities, as made to the Committee by the College Investment Counselor. This portion of the report was approved by resolution. . . .

DR. BROWER (continuing): Certain recommendations which have been made by Drexel & Co. of March 10, 1949, as to sales and purchases have been certified by the Committee on Finance, and Mr. Loveland has been empowered to carry out these recommendations:

We would like to call your attention to General Comments and Comparisons:

	1947	*1948*
Annual Dues	$ 53,516.25	$ 55,183.31
Initiation Fees	15,538.67	15,051.33
ANNALS, Subscriptions	62,435.59	70,335.02
ANNALS, Advertising	26,226.07	22,822.72
ANNALS, Expenses	57,319.32	73,106.36
Annual Session, net cost	5,135.85	16,158.88
Total Income, General Fund	194,667.35	206,200.49
Total Expenses, General Fund	151,139.01	164,385.41
Net Income, General Fund	43,528.34	41,815.08

There has been some discussion as to Life Membership Fees which might concern a group of members, because of full-time teaching or research work or employment by the Public Services, who pay annual dues of $12.00 only. However, our breakdown of this would show that it would be impossible for us to carry this without a net loss. Therefore, the Committee on Finance has recommended that Life Membership Fees remain in status quo.

. . . On motion by Dr. Brower, seconded by Dr. Hugh J. Morgan, and unanimously carried, the above recommendation concerning Life Membership Fees was approved. . . .

DR. BROWER (Continuing): The Committee on Finance took under consideration financial aid to the World Medical Association. The Committee feels highly sympathetic with this movement, but they are of the opinion that the national organization of the various countries should be responsible for any financial aid, and, therefore, they did not feel that this College should enter into any financial aid for this purpose.

. . . On motion by Dr. Brower, seconded by Dr. Ernest H. Falconer, and unanimously carried, the recommendation concerning aid to the World Medical Association was approved. . . .

DR. BROWER (Continuing): The financial aid to the Conference Committee on Graduate Training in Medicine was considered and discussed at some length. The College is highly in accord with the aims and operations of this Conference Committee, and we wish to coöperate with our members on this Committee in every way possible. We recommend to the Board of Regents that at this time we contribute $2,500.00 this year in the support of this work.

. . . On motion by Dr. Brower, seconded and regularly carried, the recommendation to contribute $2,500.00 during 1949 in aid of the Conference Committee on Graduate Training in Medicine was approved. . . .

DR. BROWER (Continuing): This Committee has some concern about the tremendous increase in guest registration at the Annual Sessions. This year we believe there are already 1,500 or 1,600 non-member guests. Heretofore, non-members have been able to come to our meetings, register, pay a $15.00 fee, and have the advantages of the meeting, receive the ANNALS for a year, and in other respects in a large measure enjoy the same position as a member of the College. Therefore, the Committee on Finance recommends to the Board of Regents that the guest fee at the Annual Sessions be increased from $15.00 to $25.00 in the future.

. . . The motion was made by Dr. Brower, regularly seconded and opened for discussion. . . .

Dr. William D. Stroud inquired about its application to medical students. It was pointed out that medical students are admitted free, if they present a matriculation card for their institution, but admission is very largely restricted to graduate medical students.

. . . The motion was put to vote and carried. Also on motion by Dr. Hugh J. Morgan, seconded by Dr. George F. Strong, and regularly carried, the report of the Committee on Finance was accepted as a whole. . . .

PRESIDENT PALMER: We shall now have the report of the Committee on Public Relations. Since the Chairman, Dr. Ernest E. Irons, is not present, Dr. George F. Strong will present their prepared report.

DR. GEORGE F. STRONG: The Committee on Public Relations met at the Waldorf-Astoria Hotel, New York, N. Y., March 28, 1949, at 11:00 a.m.

I. Fees and Dues Cases:

. . . The cases of seven Fellows who were incapacitated due to illness were reviewed, and by individual resolutions their dues were waived until recovery and resumption of practice or other remunerative work. . . .

II. Resignations:

The Committee has reviewed the resignations of the following, and recommends acceptance:

Dr. Elbert B. Agnor (Associate), Atlanta, Ga.
Dr. Joseph C. Bell (Fellow), Louisville, Ky.
Dr. Rexford W. Finegan (Associate), New York, N. Y.
Dr. Edward A. Hagmann (Associate), Billings, Mont.
Dr. George C. Ham (Associate), Chicago, Ill.
Dr. Melvin H. Knoepp (Associate), La Jolla, Calif.
Dr. Clarence W. LeDoux (Associate), Baltimore, Md.
Dr. Hugh Macdonald (Associate), Peoria, Ill.
Dr. H. Vernon Madsen (Associate), Ottawa, Ill.
Dr. Joseph A. Resch (Associate), Minneapolis, Minn.
Dr. James W. H. Rouse (Associate), San Antonio, Tex.

. . . On motion by Dr. Strong, seconded and voted upon, the above resignations were accepted. . . .

III. Delinquent Member:

. . . In accordance with conditions of the By-Laws, one Associate who was delinquent in dues for over two years was dropped from the membership roster. . . .

IV. Unfinished Business:

. . . The disciplinary case of a Fellow was reported upon, discussed and recorded as closed. . . .

(The Chairman, continuing his report—)

American Board of Internal Medicine—re Certification of Physicians from Panama and other Central American countries and their subsequent membership in the College.

The Committee on Public Relations previously reviewed this situation and we now have a final report. The original situation was brought up by the Governor for Panama, who pointed out that under the requirement that an Associate must attain certification before advancement to Fellowship, only candidates for Direct Fellowship could be presented from among native physicians in Latin American countries, due to the fact that they were not eligible to admission to A.B.I.M. examinations.

A report from Dr. Werrell, February 24, 1949, confirms this situation, if the candidate is not a citizen of the United States or Canada. It would not exclude any citizen of these countries if he were located in a Central American country, but it does exclude all native physicians. The College for many years has been on record as admitting physicians from any North American country so long as they speak English and present necessary credentials.

Certification was later added to the requirements, and it in effect excludes all candidates from Cuba and Central American countries, including Mexico, except those who can qualify for Direct Fellowship.

This involves question of policy of the College:

(1) as to whether rules for promotion of Associate to Fellow for persons not citizens of the United States or Canada should be applied to them;

(2) whether a Governor should be maintained in areas where candidates can qualify only for Direct Fellowship.

. . . President Palmer asked for opinions from the Board. . . .

Dr. Piersol said amendments to the By-Laws would be required. A motion was made that the matter be referred first to the Committee on Credentials, and if changes in the By-Laws were required, that Committee should refer it to the Committee on Constitution and By-Laws.

The motion was seconded, voted upon and carried.

Dr. Strong (Continuing): A communication was received from Dr. Eugene P. Campbell, F.A.C.P., Rio de Janeiro, Brazil, S.A., discussing the matter of abstracting medical articles from the Annals of Internal Medicine for appearance in Spanish language medical journals, and the Committee recommends this communication be referred to the Committee on the Annals of Internal Medicine.

. . . On motion by Dr. Strong, regularly seconded and carried, the report of the Committee on Public Relations was adopted. . . .

President Palmer called for the report from the American Board of Internal Medicine by Dr. Hugh J. Morgan.

Dr. Hugh J. Morgan: Mr. Chairman and Gentlemen: During 1948 a total of 1,043 candidates were admitted to the written examination by the American Board of Internal Medicine; 624 passing, and 419 failing; the percentage of failures was 40%. During 1948 a total of 741 candidates were admitted to oral examinations; 43 passing, and 248 failing; a percentage of failures of 33.4%. As of January 1, 1949, there have been 5,500 candidates certified by this Board, and of this number 1,945 were certified without examination. During 1948, 14 men were certified in Allergy, as a subspecialty; 29 in Cardiovascular Diseases, 16 in Gastro-enterology, and 7 in Tuberculosis. As of December 1, 1948, the following total number had been certified in the sub-specialties: Allergy, 120; Cardiovascular Diseases, 411; Gastro-enterology, 224; Tuberculosis, 187. During the year two regular examinations and three regional examinations were given by the Board, and oral examinations were held in San Francisco, Chicago and Philadelphia. The backlog of eligible candidates, as of July 1, 1948, is estimated to be 58; therefore, the Board is caught up with its job, in terms of the backlog.

The Board had representation through its Chairman at a meeting of the Advisory Board for Medical Specialties. We feel there is a tremendous job that must be done in the field of certification, that actually the eighteen or twenty boards are all operating blindly, without knowledge of what they are doing in terms of demands, needs, influence on practice and influence on medical education. This is a stupid thing to be happening in American medicine—that this all important business of American Boards should be going the way it is, with no facts, with no knowledge. For instance, what is an intelligent guess as to the needs for interns in the United States? No one knows. Someone must be employed who will work out the answers to many questions and problems. It is perfectly clear that the Advisory Board for Medical Specialties, which is made up from members of all of these Boards, is the organization to do that, and the American Board of Internal Medicine has urged that this Advisory Board employ a full-time staff to carry on research in this field, with relation to personnel, content of examinations, etc. The whole operation that has come into being in the last few years was given such a free-for-all official impetus by the war, and which now is on the verge of running away with postgraduate medical education and with hospital administration, has no brakes. Some board made up of a group of amateurs may get an idea that they want to do something, and there is nothing to stop them.

New Officers for the American Board of Internal Medicine, as of July 1, 1949, will be:

Dr. Truman G. Schnabel, Philadelphia, Pa. ..... Chairman
Dr. Marion A. Blankenhorn, Cincinnati, Ohio ..... Vice-Chairman
Dr. Virgil P. Sydenstricker, Augusta, Ga. ..... Secretary-Treasurer
Dr. William A. Werrell, Madison, Wis. .... Assistant Secretary-Treasurer

Reappointees from the Board of Regents of the American College of Physicians are Dr. Roy W. Scott, of Cleveland, Ohio, and Dr. Walter L. Palmer, of Chicago, Ill., each to serve an additional term of three years, through June 30, 1952. Appointees from the Section on Medicine of the American Medical Association will be announced later.

As to Board finances—the total receipts for the year 1948, $43,168.00; total deposits, $46,600.00; disbursements, $42,000.00; checkbook balance, as of January 1, 1949, $4,500.00; total assets of the Board, $110,000.00.

. . . On motion by Dr. Reginald Fitz, seconded by Dr. Alex. M. Burgess, and regularly carried, the report was accepted. . . .

President Palmer then called for the report of the Committee on Advertisements and Commercial Exhibits, Dr. George Morris Piersol, Chairman.

Dr. George Morris Piersol: At the last meeting of the Board of Regents, this Committee was empowered to investigate the matter of advertisements in the Annals of Internal Medicine and to report at this meeting. The Committee had previously requested some degree of latitude in accepting advertising. According to the rules of the Board of Regents up to the present, the Committee is restricted to those preparations which are approved by the Council on Pharmacy and Chemistry of the American Medical Association. There are a great many products which are perfectly legitimate and whose advertising could be carried without detriment which are not council-accepted, because of certain technicalities that exist in the rules and regulations of the Council. In order to benefit from the advice and knowledge of an expert, President Palmer appointed Dr. Chester S. Keefer to sit in with the Committee on Advertisements. The Committee held a meeting on February 26, and the whole matter was thoroughly discussed. Commercial exhibitors and advertisers are retrenching and are no longer willing to advertise in the free and easy way they did for some years following the war. Exceptionally few, if any, journals have had the retrictions that have been applied to the Annals. Our regulations about advertising are actually more rigid than those of the American Medical Association. It is because we will not accept for advertising certain products which they accept. It was brought out that the Annals desires to obtain more legitimate advertising, for the advertising income is now steadily falling. Our whole question is to get a little more latitude in our ability to select advertising from certain pharmaceutical houses. Dr. Keefer explained the whole situation regarding council-accepted products. He was much in sympathy with our feeling, because, as he pointed out, many articles will never be council-accepted because of such technicalities as the type of name they use. Furthermore, whereas at one time the Council on Pharmacy and Chemistry was the only body to pass on pharmaceutical products, now many Government agencies, such as the Pure Food and Drug Administration, the Bureau of Standards, and other departments, are taking over that work.

The Committee, after thorough discussion, came to the unanimous conclusion that the present rigid policy of excluding from the Advertising Section of the Annals of Internal Medicine all but council-accepted drugs should be modified to permit the acceptance of such drug products as the Committee on Advertising and Exhibits may unanimously approve. Your Chairman was asked to report this recommendation to the Board of Regents at this meeting, and to recommend that the Regents modify their present rule, to allow some latitude and some freedom of action on the part of the Committee in selecting advertising for the Annals, providing the Committee is unanimous in its action.

. . . Acceptance of this recommendation was moved by Dr. Piersol, and seconded by Dr. George F. Strong, and then opened for discussion. . . .

Chairman Palmer inquired whether the increase in latitude would in any way reflect or work a detriment to the work of the Council. He said he knew that the Food and Drug Administration was taking over many of the functions which the Council formerly performed. He had himself been at one time a member of the Council, but,

on the other hand, said that Dr. Keefer is now an active member of the Council and his advice should be dominant.

Dr. Piersol said he did not think the action recommended would be inhibiting or would do anything inimical to the Council. He said that Dr. Keefer believed there are a great many widely accepted products which everybody uses, but which the Council, because of its technical rules, could not or would not approve. For instance, the various types of penicillin—some drug houses use a trade name, such as crystacillin. Their products meet the standards laid down by the Pure Food and Drug Administration, but the name of "penicillin" only would be accepted by the Council.

. . . The motion was put to a vote and unanimously carried. . . .

On motion by Dr. Cyrus C. Sturgis, seconded by Dr. Reginald Fitz, and carried, the Committee on Fellowships and Awards was authorized to select the Latin-American fellows and also to select the places where they are to go, carrying out full authority indicated in the proposal previously approved by the Board of Regents.

At this point, Dr. Sturgis brought up the question of the possibilities of the College holding some future meeting in Detroit, saying that while their physical facilities for meeting hall may be inadequate, there is an enthusiastic group of members of the College in Michigan who undoubtedly would like to entertain the College at some future time.

Dr. Walter B. Martin asked for discussion, and not necessarily action, on the desirability of extending the medical school term to four full quarters in as many of the medical schools as possible, the purpose being to help obtain a larger number of doctors to meet the immediate shortage. The matter had come up before a commission that the Governor of Virginia appointed, and that commission believes it is the only way that a larger number of doctors can be trained reasonably soon, without very large capital outlay.

Dr. Martin said it has the advantage of being an elastic program, not involving permanent extension of facilities, but simply the addition of another quarter of teaching, and that it would be possible to initiate it and at any time that the supply of doctors appeared adequate it could be changed. He said the pressure for a larger number of physicians is quite great and real in many sections. In view of the fact that there is no present way of controlling the distribution of physicians, producing more doctors would appear to be a possible solution. The commission felt it would be possible and feasible, provided additional funds were made available to the schools to enlarge their faculties, particularly in the lower echelons, and providing that the practices or the problems that arose during the accelerated program would not prevail under this program.

Dr. Sturgis stated that at the University of Michigan it is anticipated increasing the enrollment from 140 to 190 students. They had discussed the quarter system, but met with very violent opposition, particularly from the preclinical year men who work only eight months out of the year. The last two years, of course, the faculty work all the time anyway. The consensus at Michigan was that they ought to be producing more doctors by increasing the number of medical students, and this would be possible if they receive more money for facilities for the pre-clinical years, and then they would simply teach sections in the summer without going on a formal four-quarter system.

Dr. Sturgis expressed the personal opinion that there should be more doctors, and that every medical school should expand somewhat. He pointed out that they have something like 1,300 applicants for 140 places in their freshman class.

Dr. Martin stated that they had found in Virginia that there were as many students from the state going out to other states for their training as they have students coming to Virginia for training. They had also determined that there was a very large number of qualified applicants who could not get admission to any medical school in the United States.

Dr. Alex. M. Burgess stated that there are over twenty thousand physicians who are displaced persons in western Germany, coming from the Baltic Provinces, Poland, Czechoslovakia, Hungary and elsewhere, whose qualifications bear comparison with those from any civilized country in the world, who are going to settle throughout the world, in this country and elsewhere, when we get around to modifying our laws properly. He wished that the Board of Regents be cognizant of the fact that these physicians are available and can be used to overcome certain shortages in this country.

Dr. William S. Middleton reported that at the University of Wisconsin they have increased their enrollment from 70 to 80, but at the expense of some dilution. There has obviously been the need to consider the necessity of recruiting teaching personnel. He believed that if the quarter year-round system is adopted an institution cannot use the same staff for pre-clinical sciences. He said the accelerated program of the war period showed a very interesting decrease in efficiency of teaching, fatigue on the part of the students, and, therefore, pure acceleration is not the answer. It will, however, he pointed out, give increased numbers of physicians and may be an expedient that may have to be recalled. In that case a personnel increase of about 25% in teaching must be sought, and at present they are not available. He also referred to the "fatigue of physical plants," saying it is necessary to have at least two months in the summer period to build up the physical plant on the pre-clinical sciences. In practically all institutions physical plants had deteriorated at a considerable rate and to a level no one had anticipated. He felt the most direct attack upon this program and problem is to increase the enrollment. Ten per cent would answer the problem for this country. In Wisconsin they had found that if they could move fifty physicians from larger centers, such as Milwaukee, Madison, and some of the Lake Shore towns, to the rural areas, the immediate problem would be answered, and that aside from the increasing demands of industry, Government and insurance, distribution should be investigated very carefully, and inducements found to bring younger men into the needed areas.

Dr. Walter L. Palmer said that at the University of Chicago they hold to the quarter system still. Perhaps the supply of pre-clinical teachers was a little more elastic in Chicago than it could be in some other schools, for they had no particular difficulty with increasing the faculty for the summer quarter. Students, however, may take only three-quarters consecutively, if they so choose, nor are they prohibited from taking their whole training in successive quarters.

Adjournment.

Attest: E. R. LOVELAND,
Secretary

(To be continued)

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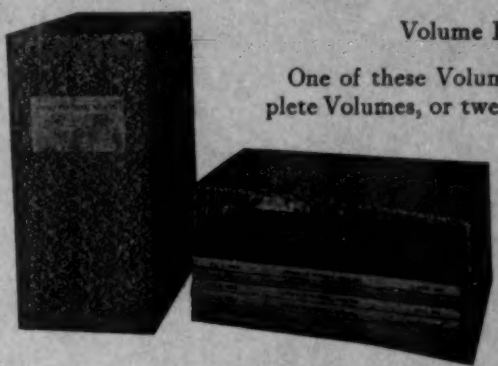

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